P1 1129791

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

February 21, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: ***60/438,563***
FILING DATE: ***January 06, 2003***
RELATED PCT APPLICATION NUMBER: *PCT/US03/39119*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

E. Bornett

E. BORNETT
Certifying Officer

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

1-9-03 60438563.0106 PPAV

Modified PTO/SB/16 (6-95)
Approved for use through 04/11/98. OMB 0651-0037
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

Docket Number	P-15463	Type a plus sign (+) inside this box –>	+

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE NAME	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Mantlo	Nathan	Bryan	Brownsburg, IN
Mayhugh	Daniel	Ray	Carmel, IN
Zhu	Guoxin		Noblesville, IN

TITLE OF THE INVENTION (280 characters max)

PYRAZOLE DERIVATIVE PPAR MODULATORS

CORRESPONDENCE ADDRESS

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

25885
PATENT TRADEMARK OFFICE

STATE	IN	ZIP CODE	46206-6288	COUNTRY	USA

ENCLOSED APPLICATION PARTS (*check all that apply*)

X	Specification	Number of pages	125		Small Entity Statement
	Drawing(s)	Number of Sheets			Other (Specify)

METHOD OF PAYMENT (*check one*)

	A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT ($)	$160.00
X	The Assistant Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 05-0840		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

[X] No.

[ ] Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,
SIGNATURE MacChan Vorndran-Jones Date 1 / 6 / 03

TYPED or PRINTED NAME MACHARRI VORNDRAN-JONES

REGISTRATION NO. (*if appropriate*) 36,711

[ ] Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FOR PATENT FILING ONLY

"Express Mail" mailing label number EL342552175US Date of Deposit 1.6.03
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Arlington, VA, 22202.

Jennifer L. Barker
Printed Name

Jennifer L Barker
Signature

PYRAZOLE DERIVATIVE PPAR MODULATORS

BACKGROUND OF THE INVENTION

Peroxisome Proliferator Activated Receptors (PPARs) are members of the nuclear hormone receptor super family, which are ligand-activated transcription factors regulating gene expression. Various subtypes of PPARs have been discovered. These include, for example, PPARα, NUC1, PPARγ and PPARδ.

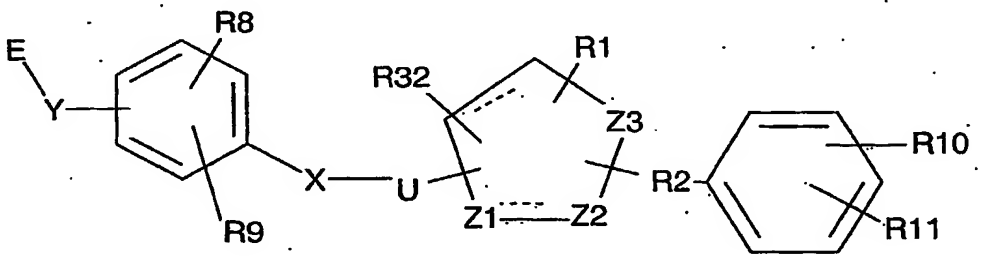
PPARα, PPARγ and PPARδ receptors have been implicated in diabetes mellitus, cardiovascular disease, obesity, Syndrome X and gastrointestinal disease, such as, inflammatory bowel disease. Syndrome X is the combination of symptoms which include hyperinsulemia combined with hypertension, elevated body weight, elevated triglycerides and elevated LDL.

Current PPAR agonist treatment for Syndrome X relates to the use of thiazolidinediones (TZDs) or other insulin sensitivity enhancers (ISEs). A need exists for new pharmaceutical agents which affect treat or prevent cardiovascular disease, particularly that associated with Syndrome X, while preventing or minimizing weight gain, and

more preferably while improving insulin sensitivity. It may be especially desirable when the active pharmaceutical agent selectively modulates a PPAR receptor subtype to provide an especially desirable pharmacological profile. In some instances, it can be desirable when the active pharmacological agent selectively modulates more than one PPAR receptor subtype to provide a desired pharmacological profile.

SUMMARY OF THE INVENTION

The present invention is directed to compounds represented by the following structural Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker may be replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with R30;

(f) Y is selected from the group consisting of C, O, S, NH and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;

(h) Z1 and Z2 are each independently selected from the group consisting of N, O, and C with the proviso that at least one of Z1 and Z2 is N;

(i) Z3 is selected from the group consisting of N, O, and C;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo; aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6

haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three independently selected from R28;

(m) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo; and

(p) ---- is optionally a bond to form a double bond at the indicated position.

In one embodiment, the present invention also relates to pharmaceutical compositions comprising at least one compound of the present invention, or a pharmaceutically

acceptable salt, solvate, hydrate, or stereioisomer thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the present invention relates to a method of selectively modulating a PPAR delta receptor by contacting the receptor with at least one compound represented by Structural Formula I, or a pharmaceutically acceptable salt, solvate, hydrate, or stereioisomer thereof.

In another embodiment, the present invention relates to a method of modulating one or more of the PPAR alpha, beta, gamma, and/or delta receptors.

In a further embodiment, the present invention relates to a method of making a compound represented by Structural Formula I.

The compounds of the present invention are believed to be effective in treating and preventing Syndrome X, Type II diabetes, hyperglycemia, hyperlipidemia, obesity, coagaulopathy, hypertension, atherosclerosis, and other disorders related to Syndrome X and cardiovascular diseases. Further, compounds of this invention can be useful for lowering fibrinogen, increasing HDL levels, treating renal disease, controlling desirable weight, treating demyelinating diseases, treating certain viral infections, and treating liver disease. In addition, the compounds can be associated with fewer clinical side effects than compounds currently used to treat such conditions.

DETAILED DESCRIPTION OF THE INVENTION

The terms used to describe the instant invention have the following meanings.

As used herein, the term "aliphatic linker" or "aliphatic group" is a non-aromatic, consisting solely of

carbon and hydrogen and may optionally contain one or more units of saturation, e.g., double and/or triple bonds (also refer herein as "alkenyl" and "alkynyl"). An aliphatic or aliphatic group may be straight chained, branched (also refer herein as "alkyl") or cyclic (also refer herein as "cycloalkyl). When straight chained or branched, an aliphatic group typically contains between about 1 and about 10 carbon atoms, more typically between about 1 and about 6 carbon atoms. When cyclic, an aliphatic typically contains between about 3 and about 10 carbon atoms, more typically between about 3 and about 7 carbon atoms. Aliphatics are preferably C_1-C_{10} straight chained or branched alkyl groups (i.e. completely saturated aliphatic groups), more preferably C_1-C_6 straight chained or branched alkyl groups. Examples include, but are not limited to methyl, ethyl, propyl, n-propyl, iso-propyl, n-butyl, sec-butyl, and tert-butyl. Additional examples include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, cyclopentyl, cyclohexylyl and the like.

The term "alkyl," unless otherwise indicated, refers to those alkyl groups of a designated number of carbon atoms of either a straight or branched saturated configuration. As used herein, "C_0 alkyl" means that there is no carbon and therefore represents a bond. Examples of "alkyl" include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-

butyl, pentyl, hexyl, isopentyl and the like. Alkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. As used herein, the term "alkyloxo" means an alkyl group of the designated number of carbon atoms with a "=O" substituent.

The term "alkenyl" means hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon double bond, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, vinyl, alkyl, 2-butenyl and the like. Alkenyl as defined above may be optionally substituted with designated number of substituents as set forth in the embodiment recited above.

The term "alkynyl" means hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon triple bond, which may occur at any point along the chain. Example of alkynyl is acetylene. Alkynyl as defined above may be optionally substituted with designated number of substituents as set forth in the embodiment recited above.

The term "heteroalkyl" refers to a means hydrocarbon chain of a specified number of carbon atoms wherein at least one carbon is replaced by a heteroatom selected from the group consisting of O, N and S.

The term "cycloalkyl" refers to a saturated or partially saturated carbocycle containing one or more rings of from 3 to 12 carbon atoms, typically 3 to 7 carbon atoms. Examples of cycloalkyl includes, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and the like. "Cycloalkyaryl" means that an aryl is fused with a cycloalkyl, and "Cycloalkylaryl-alkyl"

means that the cycloalkylaryl is linked to the parent molecule through the alkyl. Cycloalkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "halo" refers to fluoro, chloro, bromo and iodo.

The term "haloalkyl" is a C_1-C_6 alkyl group, which is substituted with one or more halo atoms selected from F, Br, Cl and I. An example of a haloalkyl group is trifluoromethyl (CF_3).

The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like. Alkoxy as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "haloalkyloxy" represents a C_1-C_6 haloalkyl group attached through an oxygen bridge, such as OCF_3. The "haloalkyloxy" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "aryl" includes carbocyclic aromatic ring systems (e.g. phenyl), fused polycyclic aromatic ring systems (e.g. naphthyl and anthracenyl) and aromatic ring systems fused to carbocyclic non-aromatic ring systems (e.g., 1,2,3,4-tetrahydronaphthyl). "Aryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "arylalkyl" refers to an aryl alkyl group which is linked to the parent molecule through the alkyl group, which may be further optionally substituted with a

designated number of substituents as set forth in the embodiment recited above. When arylalkyl is arylC_0alkyl, then the aryl group is bonded directly to the parent molecule. Likewise, arylheteroalkyl means an aryl group linked to the parent molecule through the heteroalkyl group.

The term "acyl" refers to alkylcarbonyl species.

The term "heteroaryl" group, as used herein, is an aromatic ring system having at least one heteroatom such as nitrogen, sulfur or oxygen and includes monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from the group consisting of O, N, and S. The "heteroaryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heteroaryl are, but are not limited to, furanyl, indolyl, thienyl (also referred to herein as "thiophenyl") thiazolyl, imidazolyl, isoxazoyl, oxazoyl, pyrazoyl, pyrrolyl, pyrazinyl, pyridyl, pyrimidyl, pyrimidinyl and purinyl, cinnolinyl, benzofuranyl, benzothienyl, benzotriazolyl, benzoxazolyl, quinoline, isoxazolyl, isoquinoline and the like. The term "heteroarylalkyl" means that the heteroaryl group is linked to the parent molecule through the alkyl portion of the heteroarylalkyl.

The term "heterocycloalkyl" refers to a non-aromatic ring which contains one or more oxygen, nitrogen or sulfur and includes a monocyclic, bicyclic or tricyclic non-aromatic ring of 5 to 14 carbon atoms containing one or more heteroatoms selected from O, N or S. The "heterocycloalkyl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heterocycloalkyl

include, but are not limited to, morpholine, piperidine, piperazine, pyrrolidine, and thiomorpholine. As used herein, alkyl groups include straight chained and branched hydrocarbons, which are completely saturated.

As used herein, the phrase "selectively modulate" means a compound whose EC50 for the stated PPAR receptor is at least ten fold lower than its EC50 for the other PPAR receptor subtypes.

When a compound represented by Structural Formula I has more than one chiral substituent it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated using methods familiar to the skilled artisan. The present invention includes each diastereoisomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in zwitterionic form and the present invention includes each zwitterionic form of compounds of Structural Formula I and mixtures thereof.

"Pharmaceutically-acceptable salt" refers to salts of the compounds of the Structural Formula I which are considered to be acceptable for clinical and/or veterinary

use. Typical pharmaceutically-acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an organic or inorganic base. Such salts are known as acid additiona salts and base addition salts, respectively. It will be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmaceutically-acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. These salts may be prepared by methods known to the skilled artisan.

The term, "active ingredient" means the compounds generically described by Structural Formula I as well as the sterioisomers, salts, solvates, and hydrates,

The term "pharmaceutically acceptable" means that the carrier, diluent, excipients and salt are pharmaceutically compatible with the other ingredients of the composition. Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well known and readily available ingredients.

"Preventing" refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein. The term "preventing" is particularly applicable to a patient that is susceptible to the particular patholical condition.

"Treating" refers to mediating a disease or condition and preventing, or mitigating, its further progression or ameliorate the symptoms associated with the disease or condition.

"Pharmaceutically-effective amount" means that amount of active ingredientit, that will elicit the biological or medical response of a tissue, system, or mammal. Such an

amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount when administered prophylactically to a patient can also be effective to prevent or lessen the severity of the mediated condition. Such an amount is intended to include an amount which is sufficient to modulate a selected PPAR receptor or to prevent or mediate a disease or condition. Generally, the effective amount of a Compound of Formula I will be between 0.02 through 5000 mg per day. Preferably the effective amount is between 1 through 1,500 mg per day. Preferably the dosage is from 1 through 1,000 mg per day.

The desired dose may be presented in a single dose or as divisded doses administered at appropriate intervals.

A "mammal" is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice, and rats.

Administration to a human is most preferred. The compounds and compositions of the present invention are useful for the treatment and/or prophylaxis of cardiovascular disease, for raising serum HDL cholesterol levels, for lowering serum triglyceride levels and for lower serum LDL cholesterol levels. Elevated triglyceride and LDL levels, and low HDL levels, are risk factors for the development of heart disease, stroke, and circulatory system disorders and diseases.

The compounds and compositions of the present invention are also useful for treating and/or preventing obesity.

Further, these compounds and compositions are useful for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus (NIDDM) with reduced or no body

weight gains by the patients. Furthermore, the compounds and compositions of the present invention are useful to treat or prevent acute or transient disorders in insulin sensitivity, such as sometimes occur following surgery, trauma, myocardial infarction, and the like. The physician of ordinary skill will know how to identify humans who will benefit from administration of the compounds and compositions of the present invention.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or non-human mammal which comprises administering an effective amount of active ingredient, as defined herein, to a hyperglycemic human or non-human mammal in need thereof.

The invention also relates to the use of a compound of Formula I as described above, for the manufacture of a medicament for treating a PPAR receptor mediated condition.

A therapeutically effective amount of a compound of Structural Formula I can be used for the preparation of a medicament useful for treating Syndrome X, diabetes, treating obesity, lowering tryglyceride levels, lowering serum LDL levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing atherosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. In general, a therapeutically effective amount of a compound of the present invention typically reduces serum triglyceride levels of a patient by about 20% or more, and increases serum HDL levels in a patient. Preferably, HDL levels will be increased by about 30% or more. In adition, a therapeutically effective amount of a compound, used to prevent or treat NIDDM, typically reduces serum glucose

levels, or more specifically HbA1c, of a patient by about 0.7% or more.

When used herein Syndrome X includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidemia, hyperglycemia obesity, coagulopathy, hypertension and other complications associated with diabetes. The methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any combination of the following: pre-diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, Type II or non-insulin dependent diabetes, dyslipidemia, hyperglycemia, obesity and the complications associated with diabetes including cardiovascular disease, especially atherosclerosis.

The compositions are formulated and administered in the same general manner as detailed herein. The compounds of the instant invention may be used effectively alone or in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage composition which contains a compound of Structural Formula I, a stereoisomer, salt, solvate and/or hydrate thereof ("Active Igredient") and one or more additional active agents, as well as administration of a compound of Active Ingredient and each active agent in its own separate pharmaceutical dosage formulation. For example, an Active Ingredient and an insulin secretogogue such as biguanides, thiazolidinediones, sulfonylureas, insulin, or α-glucosidose inhibitors can be administered to the patient together in a single oral dosage composition such as a tablet or capsule,

or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, an Active Ingredient and one or more additional active agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

An example of combination treatment or prevention of atherosclerosis may be wherein an Active Ingredient is administered in combination with one or more of the following active agents: antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin, and the like. As noted above, the Active Ingredient can be administered in combination with more than one additional active agent.

Another example of combination therapy can be seen in treating diabetes and related disorders wherein the Active Ingredient can be effectively used in combination with, for example, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, other insulin secretogogues, insulin as well as the active agents discussed above for treating atherosclerosis.

The Active Ingredients of the present invention, have valuable pharmacological properties and can be used in pharmaceutical compositions containing a therapeutically effective amount of Active Ingredient of the present invention, in combination with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material and other conventional

adjuvants. Proper formulation is dependent upon the route of administration chosen. Pharmaceutical compositions typically contain from about 1 to about 99 weight percent of the Active Ingredient of the present invention.

Preferably, the pharmaceutical formulation is in unit dosage form. A "unit dosage form" is a physically discrete unit containing a unit dose, suitable for administration in human subjects or other mammals. For example, a unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the Active Ingredient of the present invention, calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically-acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1500 milligrams or more according to the particular treatment involved. It may be preferred that the unit dosage is from about 1 mg to about 1000 mg.

The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts, in view of a variety of factors, including, without limitation, the species, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed, and the like.

Advantageously, compositions containing the compound of Structural Formula I or the salts thereof may be provided in dosage unit form, preferably each dosage unit containing from about 1 to about 500 mg be administered although it will, of course, readily be understood that the amount of

the compound or compounds of Structural Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances.

Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

Suitable routes of administration of pharmaceutical compositions of the present invention include, for example, oral, eyedrop, rectal, transmucosal, topical, or intestinal administration; parenteral delivery (bolus or infusion), including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. The compounds of the invention can also be administered in a targeted drug delivery system, such as, for example, in a liposome coated with endothelial cell-specific antibody.

Solid form formulations include powders, tablets and capsules.

Sterile liquid formulations include suspensions, emulsions, syrups, and elixirs.

Pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

The following pharmaceutical formulations 1 and 2 are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg .

In yet another embodiment of the compounds of the present invention, the compound is radiolabelled, such as with carbon-14, or tritiated. Said radiolabelled or tritiated compounds are useful as reference standards for in vitro assays to identify new selective PPAR receptor agonists.

The compounds of the present invention can be useful for modulating insulin secretion and as research

tools. Certain compounds and conditions within the scope of this invention are preferred. The following conditions, invention embodiments, and compound characteristics listed in tabular form may be independently combined to produce a variety of preferred compounds and process conditions. The following list of embodiments of this invention is not intended to limit the scope of this invention in any way.

Some prefered characteristics of compounds of formula I are:

(a) R3 is methyl;

(b) R4 is hydrogen;

(c) R3 and R4 are each hydrogen;

(d) R3 and R4 are each methyl;

(e) A is carboxyl;

(f) X is -O-;

(g) X is -S-;

(h) U is CH;

(i) U is CH_2CH;

(j) R9 is methyl;

(k) R9 is hydrogen;

(l) R9 is C_1-C_3 alkyl;

(m) R8 is methyl;

(n) R8 and R9 are each hydrogen;

(o) R10 is CF_3;

(p) R10 is haloalkyl;

(q) R10 is haloalkyloxy;

(r) R11 is hydrogen

(s) R10 and R11 are each hydrogen;

(t) R11 is haloalkyl;

(u) Z3 is N;

(v) Z2 and Z3 are each N;

(w) R2 is bonded to Z3;

(x) Z1 is N;

(y) Z3 is O;

(z) Z1, Z2, and Z3 are each N;

(aa) Z1 and Z3 are each N and Z2 is C;

(bb) R2 is bonded to Z2;

(cc) Z1 is O, Z2 is N and Z3 is C;

(dd) R2 is bonded to Z3;

(ee) Z1 and Z3 are each N;

(ff) ---- in the five membered ring each form a double bond at the designated position in Formula I;

(gg) R1 is C_1-C_4 alkyl;

(hh) R32 is hydrogen;

(ii) R2 is a bond;

(jj) R2 is C_1-C_2 alkyl;

(kk) Y is O;

(ll) Y is S;

(mm) Y is C;

(nn) E is C(R3)(R4)A;

(oo) R3 is hydrogen;

(pp) R3 is C_1-C_2 alkyl;

(qq) R4 is C_1-C_2 alkyl;

(rr) R3 and R4 are each hydrogen;

(ss) R3 and R4 are each methyl;

(tt) A is COOH;

(uu) Aliphatic linker is saturated;

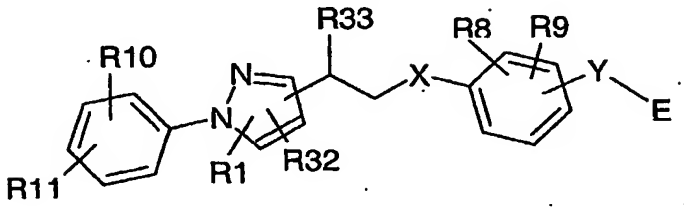
(vv) Aliphatic linker is substituted with C_1-C_3 alkyl;

(ww) Aliphatic linker is C_1-C_3 alkyl;

(xx) Aliphatic linker is C_1-C_2 alkyl;

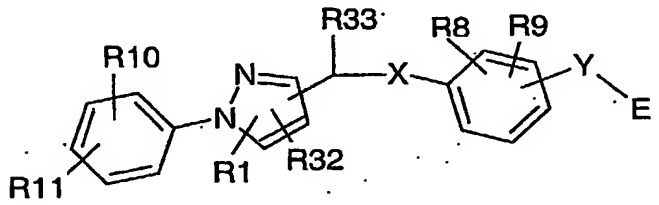
(yy) Aliphatic linker is C_1-C_3 alkyl and one carbon is replaced with an -O-;

(zz) A compound of Formula II:



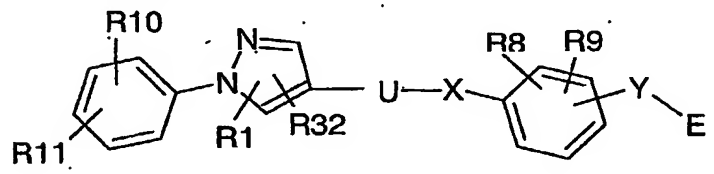
;

(aaa) A compound of Formula III:



;

(bbb) A compound of Formula IV:



;

(ccc) Aryl is a phenyl group;

(ddd) Aryl is a naphthyl group;

(eee) A compound of Formula I that selectively modulates a delta receptor;

(fff) An Active Ingredient, as described herein, that is a PPAR coagaonist that modulates a gamma receptor and a delta receptor;

(ggg) An Active Ingredient, as described herein, for use in the treatment of cardiovascular disease;

(hhh) An Active Ingredient, as described herein, for use in the treatment of Syndrome X;

(iii) An Active Ingredient for use in the control of obesity;

(jjj) An Active Ingredient for use in treating diabetes;

(kkk) An Active Ingredient that is a PPAR receptor agonist;

(lll) A compound of Formula I selected from the group consisting of

{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid;

3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid;

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenoxy)-acetic acid;

(R,S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-propionic acid;

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;

(R,S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;

(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;

(R,S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;

(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R,S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;

(3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-acetic acid;

{3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenyl}-acetic acid;

(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-acetic acid;

2-(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;

(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-acetic acid;

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;

(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;

(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;

(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;

(S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;

(R)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;

(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;

(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;

(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

{4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

{4-[1-(3,5-Bis-trifluoromethyl-phenyl)-5-methyl-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid;

3-(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid;

3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid;

{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid;

{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid;

3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid;

(S)-3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-2-methoxy-propionic acid;

{3-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid;

3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid;

3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-2-methoxy-propionic acid;

{2-Methyl-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid;

[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid;

[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid;

3-[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethoxy)-phenyl]-propionic acid;

{2-Methyl-4-[1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

{2-Methyl-4-[5-methyl-1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

{4-[1-(3,5-Bis-trifluoromethyl-benzyl)-5-phenyl-1H-[1,2,3]triazol-4-ylmethanesulfonyl]-2-methyl-phenoxy}-acetic acid;

3-(2-Methyl-4-{1-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethoxy}-phenyl)-propionic acid;

3-{2-Methyl-4-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-ylmethoxy]-phenyl}-propionic acid;

{4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid; {4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxy]-2-methyl-phenoxy}-acetic acid; and

3-{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid;

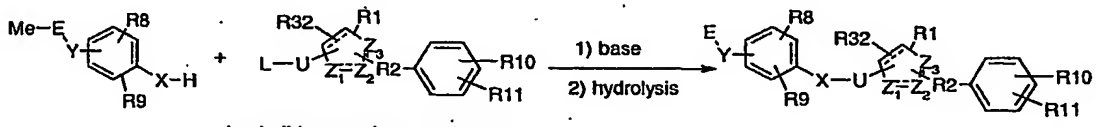
(iii) A compound of Formula I selected from the group consisting of(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid, (S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid, (R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid, (R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid, and {2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid; and

(jjj) A compound of Formula I selected from the group consisting of (R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid and {2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid.

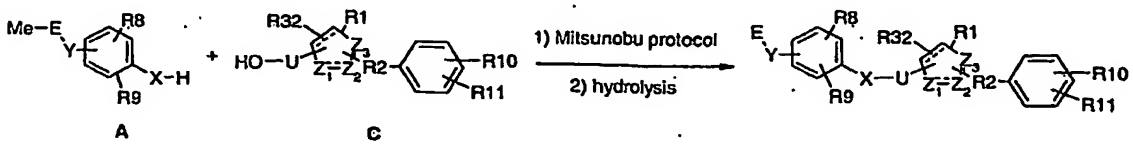
SYNTHESIS

Compounds of the present invention have been formed as specifically described in the examples. Further, many compounds are prepared as more generally using a) alkylation of phenol/thiophenol with a halide, b) a Mitsunobu protocol (O. Mitsunobu, 1981 Synthesis, p1); c) and other methods known to the skilled artisan. Alternative synthesis methods may also be effective and known to the skilled artisan.

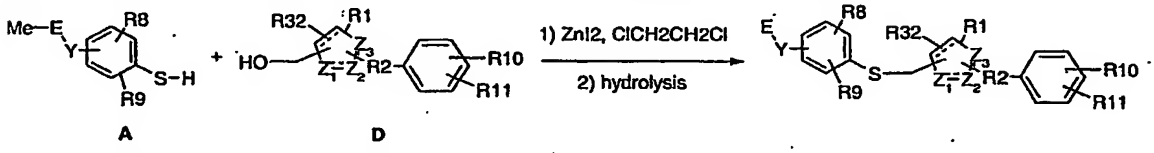
For example, an intermediate like A is alkylated with an alkylating agent B in the presence of a base (e.g. K2CO3, Cs2CO3 etc.). Hydrolysis in the presence of aqueous NaOH or LiOH gave the acid product.



Alternatively, an intermediate like A is coupled with an alcohol C under Mitsunobu reaction condition (DEAD/PPh3, ADDP/Pbu3 etc.). Hydrolysis in the presence of aqueous NaOH or LiOH gave the acid product:

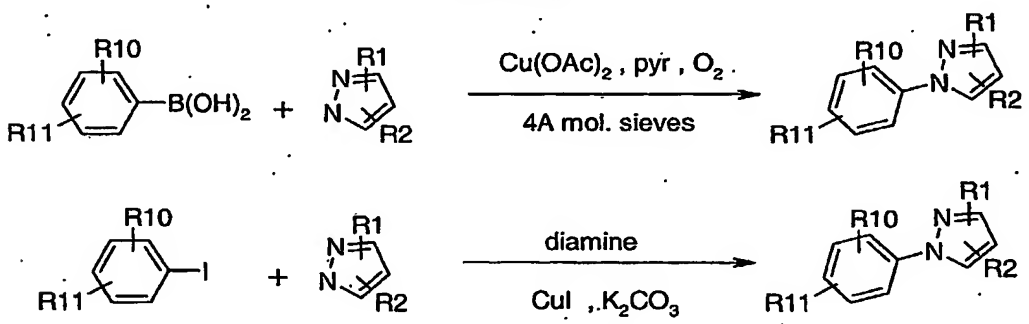


Thioether analogs could also be prepared by a ZnI2 mediated thioether formation reaction as shown below:



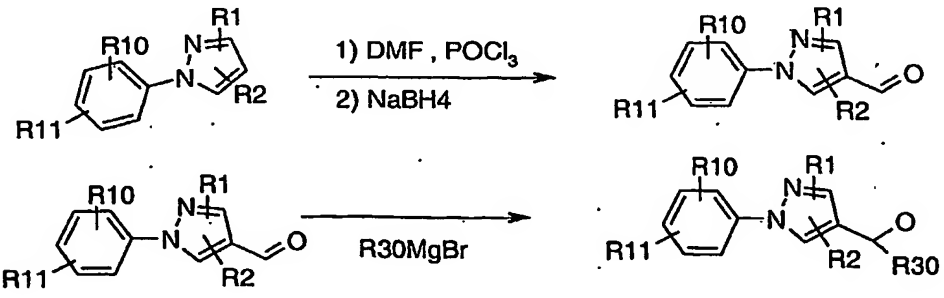
Intermediates B, C and D can be made in one of the following methods. Coupling reaction between pyrazole and aryl boronic acid or Aryl halide in the presence of copper gave the 1-arylpyrazole:

Scheme 1



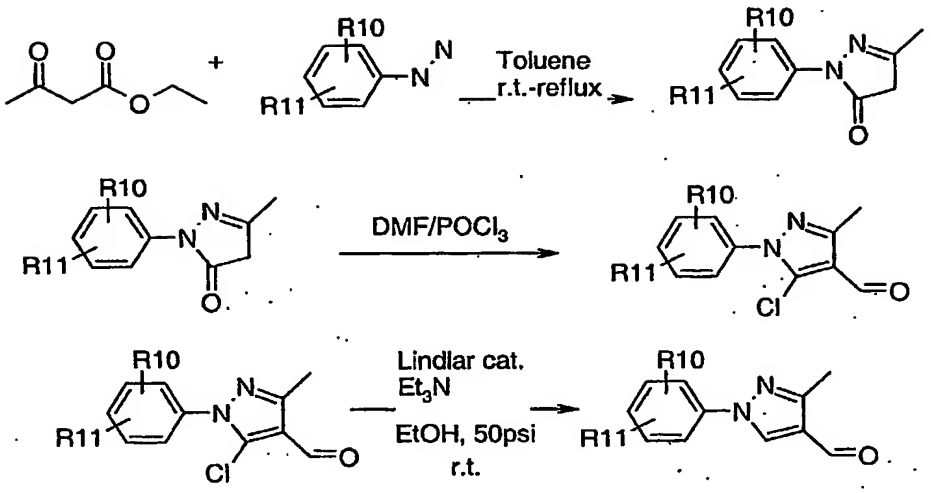
Formylation under Vilsmeier-Haack reaction condition of the 3-arylpyrazole gave the 3-formyl pyrazole, sodium borohydride reduction afforded the primary alcohol. The secondary alcohol intermediates can be obtained by alkylation with a Grignard reagent.

Scheme 2



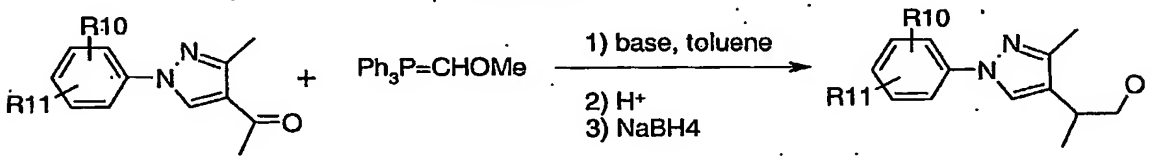
Alternatively, the pyrazole intermediates can be made by the following method starting from β-ketoesters:

Scheme 3



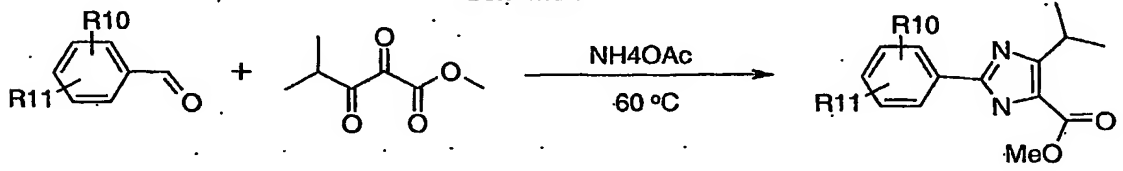
A Wittig reaction was used to extend chain at 4-position as shown in scheme 4:

Scheme 4



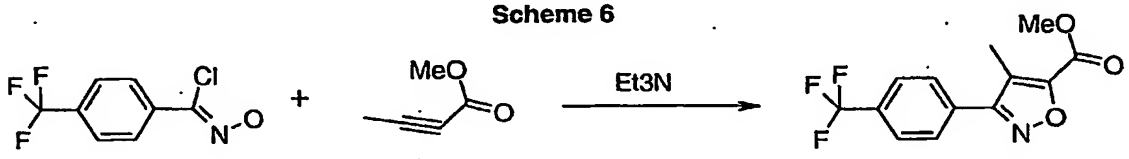
Imidazole intermediate can be made according to scheme 5:

Scheme 5



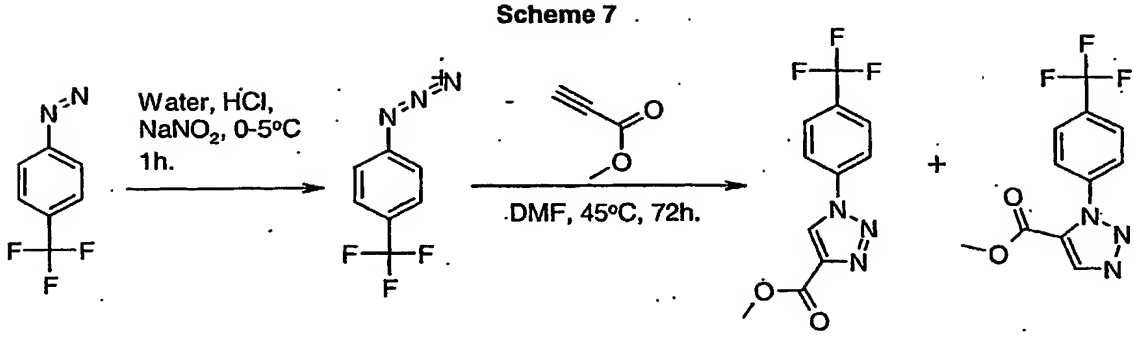
Isoxazole intermediate was obtained by the following cycloaddition reaction:

Scheme 6



Triazole intermediate can be made by the following method:

Scheme 7



EXEMPLIFICATION

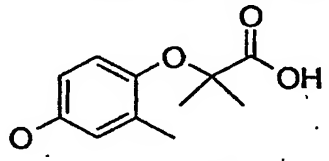
The Examples provided herein are illustrative of the invention claimed herein and are not intended to limit the scope of the claimed invention in any way.

Instrumental Analysis

Infrared spectra are recorded on a Perkin Elmer 781 spectrometer. ^{1}H NMR spectra are recorded on a Varian 400 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet and m = multiplet), integration, coupling constant (Hz) and assignment. ^{13}C NMR are recorded on a Varian 400 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm and DMSO-d_6 at 39.5 ppm). Combustion analyses are performed by Eli Lilly & Company Microanalytical Laboratory. High resolution mass spectra are obtained on VG ZAB 3F or VG 70 SE spectrometers. Analytical thin layer chromatography is performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization is accomplished with UV light.

Preparation 1

2-(4-Hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid



Step A

2-(4-Benzyloxy-2-formylphenoxy)-2-methyl propionic acid ethyl ester

5-Benzyloxy-2-hydroxy-benzaldehyde (Kappe, T.; Witoszynskyj, T. Arch. Pharm., 1975, 308 (5), 339-346) (2.28 g, 10.0 mmol), ethyl bromoisobutyrate (2.2 mL, 15 mmol), and cesium carbonate (3.26 g, 10.0 mmol) in dry DMF (25 mL) are heated at 80 °C for 18 h. The reaction mixture is cooled and partitioned between water (30 mL) and ether (75 mL). The organic layer is washed with brine (15 mL). The aqueous layers are back-extracted with ethyl acetate (30 mL), and the organic layer is washed with brine (20 mL). The combined organic layers are dried (Na_2SO_4) and concentrated to a brown oil. The crude product is purified by flash chromatography using hexanes:ethyl acetate (2.5:1) to give a pale yellow solid (3.04 g, 89%): mp 65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.1 Hz), 1.62 (s, 6H), 4.23 (q, 2H, J = 7.1 Hz), 6.81 (d, 1H, J = 8.8 Hz), 7.10 (dd, 1H, J = 4.6, 9.0 Hz), 7.30-7.43 (m, 6H); MS (ES) m/e 343.1 [M+1].

Step B

2-(4-Hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester

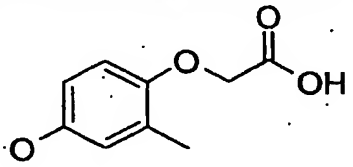
2-(4-Benzyloxy-2-formyl-phenoxy)-2-methyl-propionic acid ethyl ester (9.00 g, 26.3 mmol) in ethanol (250 mL) is treated with 5% Pd/C (1.25 g) and hydrogen (60 psi, rt, overnight). Additional 5% Pd/C (1.25 g) is added, and the reaction is continued for 6h at 40 °C. The mixture is filtered and concentrated to a tan oil (6.25 g). This oil contained 9 mol% of 2-(4-Hydroxy-2-hydroxymethyl-phenoxy)-2-methyl-propionic acid ethyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.3 Hz), 1.51 (s, 6H), 2.14 (s, 3H), 4.24

(q, 2H, J = 7.3 Hz), 5.68 (brs, 1H), 6.47 (dd, 1H, J = 3.4, 8.8 Hz), 6.59 (d, 1H, J = 8.3 Hz), 6.60 (brs, 1H).

The following compound is prepared in a similar manner:

Preparation 2

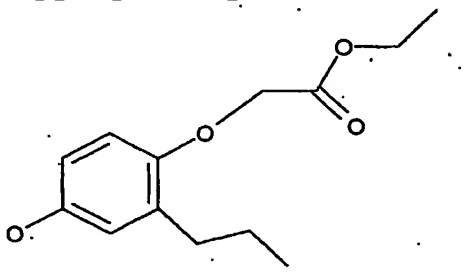
2-(4-Hydroxy-2-methyl-phenoxy)-acetic acid



^{1}H NMR (400 MHz, CDCl3) δ 1.28 (t, 3H, J = 7.1 Hz), 2.24 (s, 3H), 4.25 (q, 2H, J = 7.1 Hz), 4.55 (s, 2H), 6.56 (dd, 1H, J = 2.7, 8.5 Hz), 6.61 (d, 1H, J = 8.3 Hz), 6.65 (d, 2H, J = 2.9 Hz).

Preparation 3

(4-Hydroxy-2-propyl-phenoxy)-acetic acid ethyl ester



Step A

4-Benzyloxy-2-propylphenol

2-Allyl-4-benzyloxyphenol (WO 9728137 A1 19970807, Adams, A.D. et al.) (5.00 g, 20.8 mmol) in ethyl acetate (40 mL) is treated with 5% Pd/C (0.25 g) and hydrogen (1 atm) at ambient temperature for 18 h. The mixture is filtered and concentrated. The crude product is purified on a Biotage medium pressure chromatography system using a 40L normal phase cartridge and eluted with 10% ethyl acetate in hexanes to give a tan solid (2.8 g, 56%). Rf = 0.33 (25% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 5H),

6.78 (s, 1H), 6.69 (d, J = 1.5 Hz, 2H), 5.00 (s, 2H), 4.31 (s, 1H), 2.55 (t, J = 7.6 Hz, 2H), 1.64 (q, J = 7.5 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H).

Step B

(4-Benzyloxy-2-propylphenoxy)acetic acid ethyl ester

A solution of 4-benzyloxy-2-propylphenol (0.50 g, 1.94 mmol) in dry DMF (7 mL) is cooled in an ice bath and treated with NaH (0.15 g, 3.8 mmol, 60 % oil dispersion). The ice bath is removed, ethyl bromoacetate (0.43 mL, 3.9 mmol) is added, and the mixture is placed in an oil bath (T=85 °C). After 18 h, the reaction mixture is cooled and concentrated in vacuo. The residue is diluted with EtOAc, washed with brine (2x), dried (Na_2SO_4), and concentrated. The crude product is purified by radial chromatography using 10% ethyl acetate in hexanes to give a tan solid (0.62 g, 97%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 5H), 6.82 (d, J = 2.9 Hz, 1H), 6.72 (dd, J = 8.8, 2.9 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 5.00 (s, 2H), 4.57 (s, 2H), 4.25 (q, J = 7.0 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.64 (q, J = 7.5 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); MS (FIA) m/e 329 (M+1).

Step C

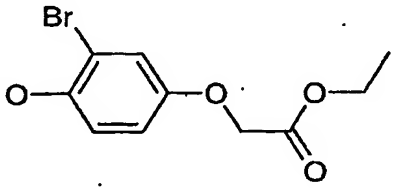
(4-Hydroxy-2-propylphenoxy)acetic acid ethyl ester

A solution of (4-benzyloxy-2-propylphenoxy)acetic acid ethyl ester (0.60 g, 1.83 mmol) in THF (15 mL) is treated with 5% Pd/C (75 mg) and hydrogen (60 psi) at ambient temperature for 24 h. The mixture is filtered and concentrated. The crude product is purified by radial chromatography using 15% ethyl acetate in hexanes to give a tan solid (0.25 g, 57%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, J = 2.9 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 6.57 (dd, J = 8.8, 2.9 Hz, 1H), 4.56 (s, 1H), 4.40 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 1.63 (q, J = 7.5 Hz,

2H), 1.29 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); MS (FIA) m/e 239 (M+1).

Preparation 4

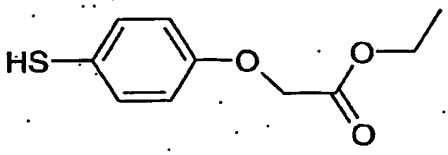
(3-Bromo-4-hydroxy-phenoxy)-acetic acid ethyl ester



To a solution of (4-hydroxy-phenoxy)-acetic acid ethyl ester (0.59 g, 3 mmol) in acetic acid (1.5 mL) is added bromine (0.48 g, 9 mmol) in acetic acid (0.5 mL) at room temperature. After 5 min, solvent is evaporated and purified by column chromatography on silica gel giving the title compound (0.6 g).

Preparation 5

(4-Mercapto-phenoxy)-acetic acid ethyl ester



Step A

(4-Chlorosulfonyl-phenoxy)-acetic acid ethyl ester

Phenoxy-acetic acid ethyl ester (9.1 mL) is added to chlorosulfonic acid (15 mL) at 0°C dropwise. The reaction is stirred at 0 °C for 30 min, it is allowed to warm to room temperature. After 2 hrs, the reaction mixture is poured into ice, solid product is collected by filtration and dried under vacuum.

Step B

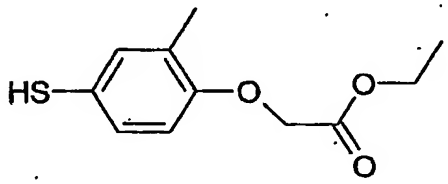
(4-Mercapto-phenoxy)-acetic acid ethyl ester

To a mixture of(4-chlorosulfonyl-phenoxy)-acetic acid ethyl ester (0.98 g, 3.5 mmol) and tin powder (2.1 g) in ethanol (4.4 mL) is added HCl in dioxane (1.0 M, 4.4 mL) under nitrogen. The mixture is heated to reflux for 2 hrs, it is poured into ice and methylene chloride and filtered. The layers are separated and extracted with methylene chloride, dried and concentrated. The crude product is used for next step without purification.

The following compounds are made in a similar manner:

Preparation 6

(4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester

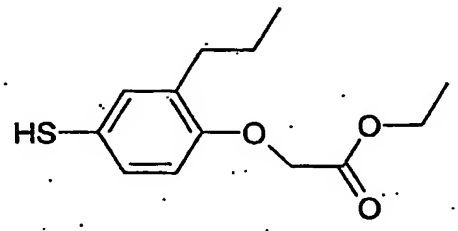


This compound can also be made by the following procedure: To a stirred suspension of Zn powder (10 µm, 78.16 g, 1.2 mol) and dichlorodimethyl silane (154.30 g, 145.02 mL, 1.2 mol) in 500 mL of dichloroethane is added a solution of (4-chlorosulfonyl-2-methyl-phenoxy)-acetic acid ethyl ester (100 g, .34 mol) and 1,3-dimethylimidazolidin-2-one (116.98 g, 112.05 mL, 1.02 mol) in 1L of DCE. Addition is at a rate so as to maintain the internal temperature at ~ 52 °C, cooling with chilled water as necessary. After addition is complete, the mixture is heated at 75 °C for 1 hour. It is then cooled to room temperature, filtered and concentrated *iv*. Add MTBE, washed twice with saturated LiCl solution , concentrate *iv* again. Take up the residue in CH_3CN, wash with hexane (4X) and concentrate *iv* to yield a biphasic mixture. Let stand in a separatory funnel and separate layers, keeping the bottom layer for product. Filtration through a plug of silica gel (1 Kg, 25% EtOAc/hexane) and subsequent concentration yields 61 g (79%) of a clear, colorless oil.

NMR (DMSO-d_6) δ 7.1 (s, 1H), 7.05 (dd, 1H), 6.75 (d, 1H), 5.03 (s, 1H), 4.75 (s, 2H), 4.15 (q, 2H), 2.15 (s, 3H), 1.2 (t, 3H).

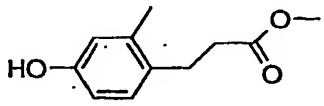
Preparation 7

(4-Mercapto-2-propyl-phenoxy)-acetic acid ethyl ester



Preparation 8

3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester



Step A

4-Bromo-3-methyl-phenyl benzyl ester

To a solution of 4-Bromo-3-methyl-phenol (20.6 g, 0.0.11 mol) in DMF (100 mL) is added Cs2CO3 (54 g, 0.165 mol), followed by benzyl bromide (14.4 mL). After stirred at 60 °C for 40 h, the reaction mixture is diluted with ethyl acetate, filtered through celite. The filtrate is washed with water and brine, dried over sodium sulfate, concentration yields the title product (27 g).

Step B

3-(4-Benzyloxy-2-methyl-phenyl)-propionic acid methyl ester

To a solution of 4-bromo-3-methyl-phenyl benzyl ester (7.6 g, 27.4 mmol) in propronitrile (200 mL) is added methyl acrylate (10 mL) and diisopropylethyl amine (9.75 mL), the solution is degassed and filled with nitrogen for three times. To this mixture are added tri-o-tolyl-phosphane (3.36

g) and palladium acetate (1.25 g) under nitrogen, then heated at 110 °C overnight, cooled to room temperature, filtered through celite. The solvent is evaporated, the residue is taken into ethyl acetate and washed with water and brine, dried over sodium sulfate. Concentration and column chromatography on silica gel eluted with hexanes and ethyl acetate yields the title compound (6.33 g).

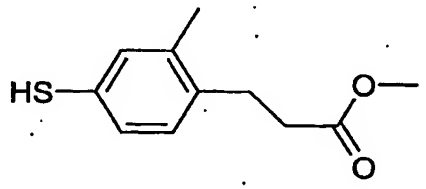
Step C

3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Benzyloxy-2-methyl-phenyl)-propionic acid methyl ester (13.7 g, 48.5 mmol) and Pd/C (5 %, 13.7 g) in MeOH (423 mL) is stirred under 60 psi of hydrogen for 24 hrs. Catalyst is filtered off, filtrate is concentrated giving the title compound (8.8 g, 93.5%).

Preparation 9

3-(4-Mercapto-2-methyl-phenyl)-propionic acid methyl ester



Step A

3-(4-Dimethylthiocarbamoyloxy-2-methyl-phenyl)-propionic acid methyl ester

3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester (5.0 g, 25.75 mmol) is dissolved into dry dioxane (100 mL) and combined with 4-dimethylamino pyridine (0.500 g, 2.6 mmol), triethylamine (7.0 mL, 51.5 mmol), and dimethylaminothiocarbomoyl chloride (4.5 g, 32.17 mmol). The reaction is heated to reflux under nitrogen. The reaction is monitored by TLC until all of the phenol is consumed, 20h. After cooling to room temperature, the reaction is diluted with ethyl acetate (200 mL). Water (75 mL) is added and the two layers are separated. The organic

layer is washed with brine (75mL) then dried over anhydrous sodium sulfate. The solvent is removed and the residue is dried under vacuum.

Step B

3-(4-Dimethylcarbamoylsulfanyl-2-methyl-phenyl)-propionic acid methyl ester

3-(4-Dimethylthiocarbamoyloxy-2-methyl-phenyl)-propionic acid methyl ester, taken crude from the previous step, is diluted with 75 mL of tetradecane and heated to reflux under nitrogen. The reaction is monitored by TLC until all the conversion is complete, 20h. The reaction is allowed to cool to room temperature, then the tetradecane is decanted away from the resulting oil. The residue is rinsed several times with hexanes. This oil is then purified using flash column chromatography, yielding 5.01 g, or 69% (2 steps) of the product.

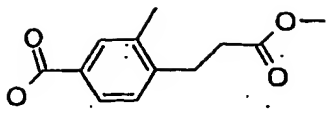
Step C

3-(4-Mercapto-2-methyl-phenyl)-propionic acid methyl ester

3-(4-Dimethylcarbamoylsulfanyl-2-methyl-phenyl)-propionic acid methyl ester (5.01 g, 17.8 mmol) is diluted with methanol (30 mL) and to this is added sodium methoxide (1.7 mL of 4M in methanol, 7.23 mmol). The reaction is heated to reflux under nitrogen and monitored by TLC. After complete conversion, 20h., the reaction is allowed to cool to room temperature. The reaction is neutralized with 1N HCl (7.23 mL) and diluted with ethyl acetate (150 mL). The two phases are separated and the organic layer is washed with water (75 mL), then brine (75 mL). The organic layer is then dried over anhydrous sodium sulfate, then concentrated to yield 4.43 g crude product that is used without further purification.

Preparation 10

4-(2-Methoxycarbonyl-ethyl)-3-methyl-benzoic acid



Step A

4-Bromo-3-methyl-benzoic acid benzyl ester

To a solution of 4-Bromo-3-methyl-benzoic acid benzyl (25.3 g, 0.118 mol) in DMF (200 mL) is added Cs2CO3 (76.6 g, 0.235 mol), followed by benzyl bromide (15.4 mL). After stirred at room temperature for 2 h, the reaction mixture is diluted with ethyl acetate, filtered through celite. The filtrate is washed with water and brine, dried over sodium sulfate, concentration yields the title product.

Step B

4-(2-Methoxycarbonyl-vinyl)-3-methyl-benzoic acid benzyl ester

To a solution of 4-bromo-3-methyl-benzoic acid benzyl ester (36 g, 118 mmol) in propronitrile (1000 mL) is added methyl acrylate (43.3 mL) and diisopropylethyl amine (42 mL), the solution is degassed and filled with nitrogen for three times. To this mixture are added tri-o-tolyl-phosphane (14.5 g) and palladium acetate (5.34 g) under nitrogen, then heated at 110 °C overnight, cooled to room temperature, filtered through celite. The solvent is evaporated, the residue is taken into ethyl acetate and washed with water and brine, dried over sodium sulfate. Concentration and column chromatography on silica gel eluted with hexanes and ethyl acetate yields the title compound (31 g, 84.7%).

Step C

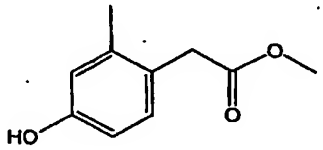
4-(2-Methoxycarbonyl-ethyl)-3-methyl-benzoic acid

A mixture of 4-(2-methoxycarbonyl-vinyl)-3-methyl-benzoic acid benzyl ester (11.6 g, 37.4 mmol) and Pd/C (5 %, 1.5 g) in THF (300 mL) and methanol (100 mL) is stirred under 60

psi of hydrogen overnight. Catalyst is filtered off, filtrate is concentrated giving the title compound (8.3 g, 100%).

Preparation 11

(4-Hydroxy-2-methyl-phenyl)-acetic acid methyl ester



Step A

4-Methoxy-2-methylbenzoic acid (2.5 g, 15.04 mmol) is stirred in thionyl chloride (50 mL) at reflux 2 hr. The mixture is concentrated and diluted with toluene (10 mL) and concentrated. The resulting solid is dried under vacuum 18 hr. The resulting acid chloride is stirred in 20 mL ether at 0 deg C. A solution of diazomethane (39.6 mmol) in ether (150 mL) is added to the acid chloride solution and stirred 18 hr. The resulting diazoketone solution is concentrated. The residue is stirred in methanol (100 mL) and a solution of silver benzoate in triethylamine (1.0 g in 10 mL) is added and the reaction is heated to 60 deg C and stirred 1 hr. The mixture is concentrated, diluted with 1.0 N aqueous hydrochloric acid (20 mL), extracted to three portions of ethyl acetate (50 mL each). The extracts are combined, washed with aqueous saturated sodium hydrogen carbonate, water, and brine (50 mL each), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is purified via silica gel chromatography eluting with 9:1 hexanes:ethyl acetate to afford 1.5 g (51%) of the homologated ester as a white solid.

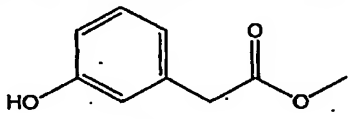
Step B

(4-Methoxy-2-methyl-phenyl)-acetic acid methyl ester (1.5 g, 7.72 mmol) is stirred in dichloromethane (50 mL) at 0 deg. C. Aluminum chloride (4.13 g, 31 mmol) is added

followed by ethane thiol (2.9 mL, 38.6 mmol). The resulting mixture is stirred at room temperature for 2 hr. Water (50 mL) is added and the product is extracted into ethyl acetate (3 X 50 ml), the extracts are combined, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford the title compound as a colorless oil, 1.4 g, 100%. MS M^++1 181. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 12

(3-Hydroxy-phenyl)-acetic acid methyl ester



Step A

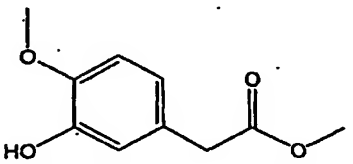
(3-Hydroxy-phenyl)-acetic acid methyl ester

(3-Hydroxy-phenyl)-acetic acid (5.0 g, 32.86 mmol) is stirred in methanol (100 mL) and concentrated (98%) sulfuric acid (3.0 mL,) is added. The mixture is heated to reflux 18 hr. The reaction is cooled and concentrated. The residue is diluted with water (100 mL) and extracted with ethyl acetate (3 X 50 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated to yield the title compound as an orange oil, 5.46 g, 100%. MS M^++1 167. The structure is confirmed by ^{1}H NMR spectroscopy.

The following compounds are made in a similar manner:

Preparation 13

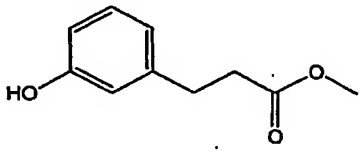
(3-Hydroxy-4-methoxy-phenyl)-acetic acid methyl ester



An orange oil. MS M^++1 197. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 14

3-(3-Hydroxy-phenyl)-propionic acid methyl ester

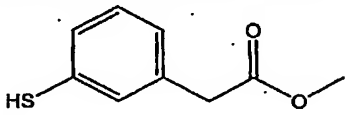


Step A

3-(3-Hydroxy-phenyl)-propionic acid methyl ester
An orange oil. MS M^++1 181. The structure is confirmed by ^1H NMR spectroscopy.

Preparation 15

(3-Mercapto-phenyl)-acetic acid methyl ester



Step A

(3-Dimethylthiocarbamoyloxy-phenyl)-acetic acid methyl ester
A mixture of (3-Hydroxy-phenyl)-acetic acid methyl ester (5.5 g, 33.1 mmol) , N,N-dimethyl thiocarbamoyl chloride (5.11 g, 41.38 mmol), triethylamine (9.2 mL, 66.2 mmol), N,N-dimethylamino pyridine (0.4 g, 3.31 mmol) and dioxane (50 mL) is stirred at reflux 18 hr. The mixture is concentrated, partioned between 1M aqueous hydrochloric acid (200 mL) and ethyl acetate (3 X 75 mL). The combined organic extracts are dried over anhydrous magnesium sulfate, filtered, concentrated, and purified via silica chromatography eluting the product with dichloromethane to afford the title compound as a brown oil, 6.8 g, 81%. MS M^++1 254. The structure is confirmed by ^1H NMR spectroscopy.

Step B

(3-Dimethylcarbamoylsulfanyl-phenyl)-acetic acid methyl ester

(3-Dimethylthiocarbamoyloxy-phenyl)-acetic acid methyl ester (6.8 g, 26.84 mmol) is stirred in tetradecane (30 mL) at 255 deg C for 8 hr. The mixture is cooled, the residue is purified by silica chromatography eluting the product with hexanes to 1:1 hexanes:ethyl acetate to afford the title compound as an orange oil, 4.9 g, 58 %. MS M^++1 254. The structure is confirmed by ^{1}H NMR spectroscopy.

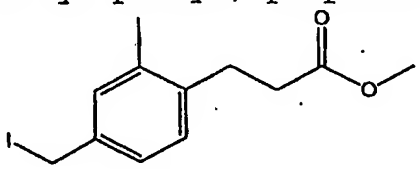
Step C

(3-Mercapto-phenyl)-acetic acid methyl ester

A mixture of (3-dimethylcarbamoylsulfanyl-phenyl)-acetic acid methyl ester (2.0 g, 7.9 mmol), potassium hydroxide (1.4 g, 24 mmol) methanol (50 mL), and water (5 mL) is stirred at reflux 3 hr. The mixture is concentrated, and product partitioned between 1M aqueous hydrochloric acid (50 mL) and ethyl acetate (3 X 75 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is taken up in methanol (50 mL), 2 mL concentrated sulfuric acid is added, and the mixture refluxed 3 hr. The mixture is concentrated, and the residue purified by silica chromatography eluting with 7:3 hexanes:ethyl acetate to afford the title compound as a pale yellow oil, 1.0 g, 69%. MS M^++1 183. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 16

3-(4-Iodomethyl-2-methyl-phenyl)-propionic acid methyl ester



Step A

3-(4-Hydroxymethyl-2-methyl-phenyl)-acrylic acid methyl ester

A mixture of methyl-4-bromo-3-methylbenzoate (5.7 g, 24.88 mmol), lithium aluminum hydride (29 mL, 29 mmol, 1 M solution in tetrahydrofuran) and tetrahydrofuran (100 mL) is stirred in ice/water for 1 hr. The reaction is quenched with aqueous hydrochloric acid (50 mL, 1 M). The product is extracted into ethyl acetate (3 X 100 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product is taken up in propionitrile (100 mL). Methylacrylate (10 mL, 121.5 mmol), palladium acetate (1.12 g, 5 mmol), tri-o-tolylphosphine (3.0 g, 10 mmol), and N,N-diisopropyl ethylamine (8.7 mL, 50 mmol) are sequentially added and the resulting reaction mixture is heated to 110 deg C 3 hr. The mixture is concentrated, and the residue diluted with aqueous hydrochloric acid (100 mL, 1M). The product is extracted with dichloromethane (2 X 100 mL) and ethyl acetate (100 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered, concentrated, and purified via silica chromatography eluting with 7:3 hexanes:ethyl acetate to 1:1 hexanes:ethyl acetate to afford the pure product as a yellow oil, 4.7 g, 91 %. MS M^++1 207. The structure is confirmed by ^{1}H NMR spectroscopy.

Step B

3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Hydroxymethyl-2-methyl-phenyl)-acrylic acid methyl ester (4.7 g, 22.8 mmol), Raney nickel (0.668 g) and tetrahydrofuran (618 mL) is shaken under 60 psig. Hydrogen 24 hr. The catalyst is filtered off, and the mixture is concentrated to afford the product as a pale yellow oil, 4.3 g, 91%. The structure is confirmed by ^{1}H NMR spectroscopy.

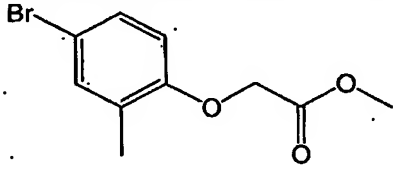
Step C

3-(4-Iodomethyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester (0.62 g, 2.98 mmol), triphenyl phosphine (0.86 g, 3.27 mmol) and dichloromethane (10 mL) is stirred at room temperature. A solution of iodine (0.83 g, 3.27 mmol) in benzene (5 mL) is added and the black mixture is stirred at room temperature 2hr. The brown mixture is diluted with 10% aqueous sodium hydrogen sulfite (5 mL) and the resulting clear mixture is washed with ethyl acetate (3 X 50 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is purified via silica chromatography eluting with 9:1 hexanes:ethyl acetate to afford the title compound as a crystalline ivory solid, 0.68g, 72%. MS M^++1 319. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 17

(4-Bromo-2-methyl-phenoxy)-acetic acid methyl ester



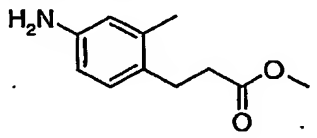
Step A

(4-Bromo-2-methyl-phenoxy)-acetic acid methyl ester

A mixture of 4-bromo-2-methylphenol (1.0 g, 5.35 mmol), sodium hydride (0.26 g, 6.42 mmol, 60% mineral oil), N,N-dimethylformamide (10 mL), and methyl-2-bromoacetate (0.56 mL, 5.88 mmol) is stirred at room temperature 18 hr. The mixture is diluted with water (50 mL) and the product extracted to ethyl acetate (3 X 50 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered, concentrated and purified via silica chromatography eluting with 8:2 hexanes:ethyl acetate to afford title compound as a colorless oil, 1.03 g, 74%. MS M^+ 259. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 18

3-(4-Amino-2-methyl-phenyl)-propionic acid methyl ester



Step A

3-(2-Methyl-4-nitro-phenyl)-acrylic acid methyl ester

To a solution of 2-bromo-5-nitrotoluene (3.11 g, 14.39 mmol) in propionitrile (105 mL) is added DIPEA (5.1 mL, 29.28 mmol). The mixture is degassed three times. Methyl acrylate (5.2 mL, 57.74 mmol) is added and the mixture is degassed. Tri-*o*-tolylphosphine (1.77 g, 5.82 mmol) and $Pd(OAc)_2$ (0.64 g, 2.85 mmol) are added and the mixture is degassed a final two times followed by heating at 110°C for 4 h. Upon cooling, the mixture is passed through Celite and the filtrate is concentrated: The residue is partitioned between Et_2O and 1N HCl. The organics are washed with saturated $NaHCO_3$ and brine, and dried with Na_2SO_4. The crude material is purified by flash chromatography to yield the title compound (2.90 g, 91%).

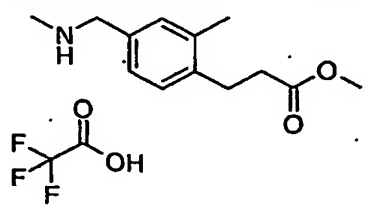
Step B

3-(4-Amino-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(2-Methyl-4-nitro-phenyl)-acrylic acid methyl ester (1.47 g, 6.64 mmol) and 5% Pd/C (0.29 g) in MeOH (100 mL) is exposed to a hydrogen atmosphere (60 psi) for 12 h. The mixture is filtered through Celite and purified by flash chromatography to yield the title compound (0.99 g, 77%).

Preparation 19

3-(2-Methyl-4-methylaminomethyl-phenyl)-propionic acid methyl ester TFA salt



Step A

3-(4-Formyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester (0.49 g, 2.35 mmol) and MnO_2 (0.80 g, 9.20 mmol) in chloroform (5 mL) is stirred at RT for 4 days. The mixture is filtered through Celite; the Celite is washed with copious amounts of EtOAc. The filtrate is concentrated and purified by flash chromatography to yield the title compound (0.29 g, 60%).

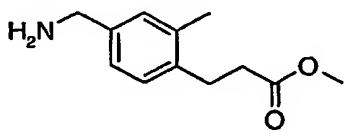
Step B

3-(2-Methyl-4-methylaminomethyl-phenyl)-propionic acid methyl ester trifluoroacetic acid

To a mixture of 3-(4-Formyl-2-methyl-phenyl)-propionic acid methyl ester (0.27 g, 1.31 mmol) and methylamine (2M in THF, 0.60 mL, 1.20 mmol) in anhydrous CH_2Cl_2 (10 mL) is added 4Å molecular sieves followed by acetic acid (0.090 mL, 1.57 mmol). The mixture is stirred at RT for 1.5 h. Sodium triacetoxyborohydride (0.39 g, 1.85 mmol) is added, and the mixture is stirred overnight. The reaction is quenched with saturated $NaHCO_3$. The organics are washed with saturated $NaHCO_3$ and brine, and dried with $MgSO_4$. Upon concentration, the mixture is purified by reverse phase chromatography to yield the title compound (0.12 g, 45%).

Preparation 20

3-(4-Aminomethyl-2-methyl-phenyl)-propionic acid methyl ester



Step A

3-(4-Chloromethyl-2-methyl-phenyl)-propionic acid methyl ester

To a 0°C solution of 3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester (1.02 g, 4.90 mmol) in anhydrous

CH_2Cl_2 (15 mL) is added triethylamine (0.75 mL, 5.38 mmol) followed by thionyl chloride (0.40 mL, 5.48 mmol). The mixture is allowed to warm to RT overnight. Water is added, and the mixture is extracted with CH_2Cl_2. The organics are dried with $MgSO_4$ and concentrated. The crude material is purified by flash chromatography to yield the title compound (1.01 g, 91%).

Step B

3-(4-Azidomethyl-2-methyl-phenyl)-propionic acid methyl ester

To a solution of 3-(4-Chloromethyl-2-methyl-phenyl)-propionic acid methyl ester (0.52 g, 2.31 mmol) in DMF (7 mL) is added sodium azide (0.25 g, 3.84 mmol). The mixture is stirred overnight. Water is added, and the mixture is extracted with EtOAc. The organics are dried with Na_2SO_4 and concentrated to yield the title compound (0.49 g, 91%). The material is used without further purification.

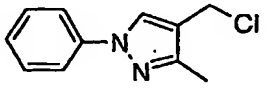
Step C

3-(4-Aminomethyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Azidomethyl-2-methyl-phenyl)-propionic acid methyl ester (0.20 g, 0.86 mmol) and 5% Pd/C (32 mg) in EtOH (50 mL) is exposed to a hydrogen atmosphere (60 psi) at RT overnight. Upon filtering the mixture through Celite, the filtrate is concentrated to yield the title compound (0.14 g, 78%). The material is used without further purification.

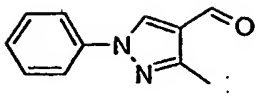
Preparation 21

4-Chloromethyl-3-methyl-1-phenyl-1H-pyrazole



Step A

3-Methyl-1-phenyl-1H-pyrazole-4-carbaldehyde



Phosphoryl chloride (2.62 g, 17.1 mmol) is added dropwise to a solution of 3-methyl-1-phenyl-1H-pyrazole (2.7 g, 17.1 mmol) in DMF (1.25 g, 17.1 mmol) at 100 °C. After heated 3hrs, the reaction mixture is cooled with ice bath and quenched by water. The resulting mixture is basified by 5N NaOH to pH = 4, extracted with ethyl acetate, dried, concentrated. Column chromatography on silica gel yields the title compound.

Step B

(3-Methyl-1-phenyl-1H-pyrazol-4-yl)-methanol

To a solution of 3-Methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (0.9 g, 4.84 mmol) in ethanol (20 mL) is added sodium borohydride (0.18 g, 4.84 mmol) at 0~5 °C, warmed to room temperature. After stirred for 2hrs, quenched by water, ethanol is evaporated. The resiude is diluted with water and extracted with ethyl acetate, dried over sodium sulfate. Concentration yields the title compound.

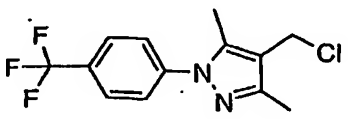
Step C

4-Chloromethyl-3-methyl-1-phenyl-1H-pyrazole

A solution of (3-methyl-1-phenyl-1H-pyrazol-4-yl)-methanol (0.7 g, 3.72 mmol) and triethyl amine (1.04 mL, 7.4 mmol) in methylene chloride (16 mL) is cooled to 0 °C, then MeSO2Cl (0.46 mL, 5.95 mmol) is added dropwise. After 4 hrs, the reaction mixture is diluted with methylene chloride and washed with sodium bicarbonate, water and brine, dried over sodium sulfate. Concentration yields the crude title compound, which is used for the next step without further purification.

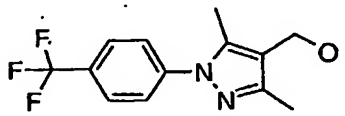
Preparation 22

4-Chloromethyl-3,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole



Step A

[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol



A THF (5 mL) solution of 3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carboxylic acid ethyl ester (1.0 g, 3.2 mmol) is cooled to 0 °C and a 1M $LiAlH_4$ (3.2 mL, 3.2 mmol) is added slowly. The reaction is warmed to room temperature slowly, after stirring at room temperature for 2 h, tlc (15% EtOAc/hexane) showed that all the starting ester had been consumed. The reaction is cooled and carefully quenched with water, 5N NaOH. The light tan solid is filter through celite and dried to give 0.86 g of the title compound.

Step B

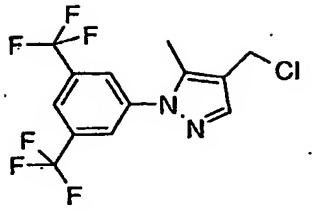
4-Chloromethyl-3,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole

A solution of [3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol (0.86 g, 3.2 mmol) and triethyl amine 0.9 mL, 6.4 mmol) in methylene chloride (16 mL) is cooled to 0 °C, then MeSO2Cl (0.4 mL) is added dropwise. After 2 hrs, TLC indicated that the reaction is not complete, 10 mol % more of triethyl amine and $MeSO_2Cl$ are added. After additional 2hrs, the reaction mixture is diluted with methylene chloride and washed with sodium bicarbonate, water and brine, dried over sodium sulfate. Concentration yields the crude title compound, which is used for the next step without further purification.

The following compounds are made in a similar manner:

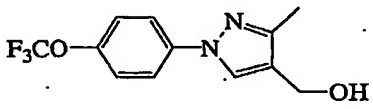
Preparation 24

1-(3,5-Bis-trifluoromethyl-phenyl)-4-chloromethyl-5-methyl-1H-pyrazole



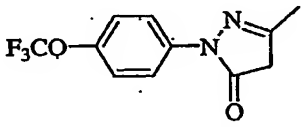
Preparation 25

[3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-methanol



Step A

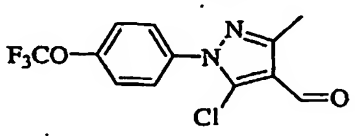
5-Methyl-2-(4-trifluoromethoxy-phenyl)-2,4-dihydro-pyrazol-3-one



To a solution of the trifluoromethoxyphenyl hydrazine HCl salt (10.36g, 45.3 mmol) and toluene (250.0mL) at room temperature is added sodium hydroxide (1.04 g). After stirred overnight, the mixture is treated with ethyl acetoacetate (48.09mL, 0.38m). Reaction mixture is then stirred at room temperature for 66 hrs, diluted with ethyl acetate, washed with water, dried over sodium sulfate. Concentration and column chromatography on silica gel yields the title compound (9.3 g).

Step B

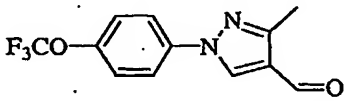
5-Chloro-3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde



To DMF (5.03 mL) at 10°C is added $POCl_3$ (6.1 mL) over a period of 30 minutes, to this solid is then added 5-Methyl-2-(4-trifluoromethoxy-phenyl)-2,4-dihydro-pyrazol-3-one (9.3 g, 32.4 mmol), followed by 5.03 mL of DMF. The reaction mixture is slowly heated to 100°C, an additional $POCl_3$ (6.1 mL) is added after 18 hrs. Heating is continued for another 6hrs before the reaction mixture is very carefully reversed quenched into crushed ice, extracted with CH_2Cl_2, washed with 2N NaOH and brine, dried over sodium sulfate. Concentration and column chromatography on silica gel eluted with hexanes/ethyl acetate yields the title compound (9.6 g).

Step C

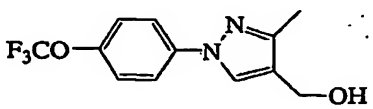
3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde



To 5-chloro-3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde (5.7 g, 17 mmol) dissolved in EtOH (188 mL) is added Et_3N (4.8 mL) and Lindlar catalyst (0.476 g). The mixture is then hydrogenated at room temperature (50psi). After 2.5 hrs, reaction mixture is the filtered through celite, concentrated to a solid. Column chromatography n silica gel eluted with hexanes/ethyl acetate yields the title compound (3.4 g, 66.5 % yiel, and [3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-methanol (0.85 g, 16.5 % yield).

Step D

[3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-methanol

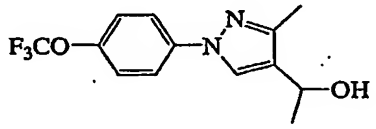


To a solution of 3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde (0.76 g, 2.55 mmol) in ethanol (10

mL) is added NaBH4 (0.1 g, 2.64 mmol). After 2hrs, the reaction is quenched by water, ethanol is evaporated and the residue is extracted with ethyl acetate, dried. Concentration yields the title compound (0.75 g).

Preparation 26

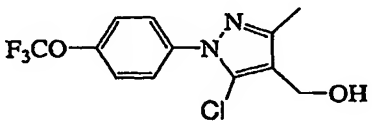
1-[3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethanol



To a solution of 3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde (3.4 g, 11.4 mmol) tetrahydrofuran (80 mL) is added methyl magnesium bromide (4.6 mL, 13.7 mmol, 3 M in ether) dropwise at 0°C, the resulting mixture is allowed to stir at room temperature 30 min. The reaction mixture is quenched by aqueous ammonium chloride (30 mL), extracted with ethyl acetate, the combined extracts are dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography on silica gel eluted with hexanes/ethyl acetate yields the title compound (3.3 g).

Preparation 27

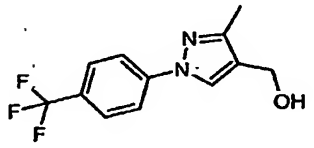
[5-Chloro-3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-methanol



To a solution of 5-chloro-3-methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazole-4-carbaldehyde (1.0 g, 3.0 mmol) in ethanol (10 mL) is added NaBH4 (0.113 g, 3 mmol). After 2hrs, the reaction is quenched by water, ethanol is evaporated and the residue is extracted with ethyl acetate, dried. Concentration yields the title compound (0.95 g).

Preparation 28

[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol



Step A

The intermediate obtained from Step A is obtained from two separate methods.

Method 1

3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole

To a solution of 4-(trifluoromethyl)phenylboronic acid (5.04g, 26.5mmol), 3-methylpyrazole (1.1ml, 13.2mmol), and pyridine (2.1ml, 26.5mmol) in dichloromethane (160ml) is added copper(II) acetate (3.61g, 19.9mmol) and 4A molecular sieves (10.0g). The suspension is stirred at ambient temperature in the open air for 48 hours, then filtered through Celite and concentrated in vacuo to a crude solid. Purification by silica flash chromatography (40:1 hexanes:ethyl acetate to 10:1 hexanes:ethyl acetate) yields the title compound as a white solid. MS: m/z (M+1) 227

Method 2

3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole

A mixture of 4-iodobenzotrifluoride (246g, 0.904mol), 3-methylpyrazole (90g, 1.09mol) and potassium carbonate (254g, 1.83mol) in 1,4-dioxane (1L) under N_2 is treated with cupric iodide (1.75g, 9.1mmol) and trans-1,2-cyclohexanediamine (7.5ml, 62.4mmol) and heated at 110°C for 30 hours. The mixture is cooled and diluted with water (1.5L) and ethyl acetate (1.5L). The organic layer is washed with water (1L) and concentrated to an oil. Purification by silica flash chromatography (4:1 hexanes:ethyl acetate) yields the title compound as a white solid. MS: m/z (M+1) 227

Step B

3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde

To a solution of 3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole (1.88g, 8.31mmol) in DMF (8.0ml) heated at 90° C is carefully added phosphorous oxychloride (1.0ml, 10.8mmol) and the resulting mixture heated at 90° C for 7 hours. Additional phosphorous oxychloride (0.75ml, 8.0mmol) is added and the mixture heated for an additional 2 hours. The mixture is cooled at 0° C, then carefully treated with cold water (75ml). After dilution with diethyl ether (40ml) to dissolve solids, the mixture is adjusted to pH 3 with 5N NaOH. The aqueous layer is extracted with diethyl ether (2 x 25ml), the organic extracts then combined and washed with water, brine, dried (Na_2SO_4) and concentrated to a crude solid. Purification by silica flash chromatography (20:1 hexanes:ethyl acetate to 5:1 hexanes:ethyl acetate) provided the title compound as a white solid. MS: m/z (M+1) 255.

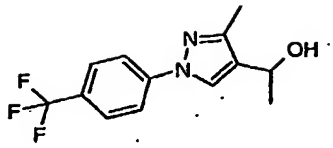
Step C

[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol

To a chilled (0°C) suspension of 3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde (350mg, 1.37mmol) in ethanol (6 ml) is added sodium borohydride (52mg, 1.37mmol) portionwise over two minutes. The reaction mixture is removed from the cold bath and stirred for one hour. After quenching with water (25ml), the reaction mixture is extracted with diethyl ether (3 x 15ml). The combined organic extracts are washed with water, brine, then dried (Na_2SO_4) and concentrated to provide the title compound as a white solid. MS: m/z (M+1) 257.

Preparation 29

1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanol

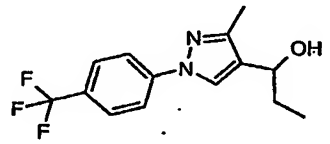


To a cooled (0°C) solution of 3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde (500mg, 1.96mmol) in tetrahydrofuran (2.5ml) is added a solution of methyl magnesium bromide (3M in diethyl ether)(0.98ml, 2.94mmol) over 4 minutes. The mixture is removed from the cold bath and stirred for two hours, then cooled again to 0°C and treated with saturated aqueous ammonium chloride (30ml) followed by water (20ml). After extraction with ethyl acetate (3 x 20ml), the combined organic extracts are washed with brine, then dried (Na_2SO_4) and concentrated to a crude solid. Purification by silica flash chromatography (20:1 hexanes:ethyl acetate to 3:1 hexanes:ethyl acetate) provided the title compound as a racemic white solid.

MS: m/z (M+1) 271.

Preparation 30

1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol

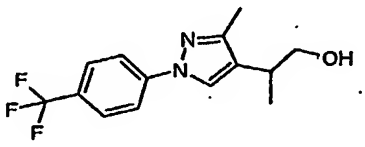


To a cooled (0°C) solution of 3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole-4-carbaldehyde (300mg, 1.18mmol) in tetrahydrofuran (3.0ml) is added a solution of ethyl magnesium bromide (3M in diethyl ether)(0.59ml, 1.77mmol) over 2 minutes. The mixture is removed from the cold bath and stirred for 3 hours, then cooled again to 0°C and treated with saturated aqueous ammonium chloride and water. After extraction with ethyl acetate (3 x 15ml), the combined organic extracts are washed with brine, then dried (Na_2SO_4) and concentrated to a crude solid. Purification by silica flash chromatography (25:1 hexanes:ethyl acetate to 4:1

hexanes:ethyl acetate) provided the title compound as a racemic white solid. MS: m/z (M+1): 285.

Preparation 51

2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol



Step A

1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone

To a solution of 1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanol (2.95g, 10.9mmol) in chloroform (80ml) is added activated manganese(IV)dioxide (9.5g, 109mmol), and the resulting suspension heated at reflux for 36 hours. The mixture is cooled and filtered through Celite, washed with chloroform, and the filtrate concentrated to a crude solid. Purification by silica flash chromatography (20:1 hexanes:ethyl acetate to 2:1 hexanes:ethyl acetate) provided the title compound as a white solid. MS: m/z (M+1) 269.

Step B

4-(2-Methoxy-1-methyl-vinyl)-3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole

A solution of potassium tert-butoxide (3.74g, 33.3mmol) in tetrahydrofuran (25ml) is added dropwise over 15 minutes to a cooled (0°C) suspension of methoxymethyltriphenylphosphonium chloride (11.41g, 33.3mmol) in tetrahydrofuran (35ml) . The mixture is stirred at 0°C for 20 minutes and then treated dropwise over 5 minutes with a solution of 1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone (3.0g, 11.1mmol) in tetrahydrofuran (20ml). After addition is complete, the mixture is removed from the cold bath and stirred for 2

hours, then diluted with brine (300ml) and diethyl ether (150ml). The organic layer is removed, and the remaining aqueous layer extracted with diethyl ether (2 x 25ml). The organic extracts are combined, washed with brine, dried (Na_2SO_4), and concentrated to an oil which is purified by silica flash chromatography (30:1 hexanes:ethyl acetate to 8:1 hexanes:ethyl acetate) to provide the title compound as an oil. MS: m/z (M+1) 297.

Step C

2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propionaldehyde

A cooled (0°C) solution of 4-(2-Methoxy-1-methyl-vinyl)-3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole (2.7g, 9.11mmol) in tetrahydrofuran (25ml) is treated dropwise over 5 minutes with concentrated hydrochloric acid (15ml) and the mixture stirred at 0°C for 3 hours. After dilution with diethyl ether (50ml), the reaction mixture is adjusted to pH 7 with 1N NaOH. The aqueous layer is extracted with diethyl ether (2 x 30ml), the organic extracts then combined and washed with brine and dried (Na_2SO_4). Concentration provided the title compound as an oil which slowly crystallized and is used without further purification. MS: m/z (M+1) 283.

Step D

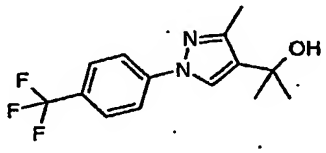
2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol

Sodium borohydride (132mg, 3.5mol) is added in one portion to a cooled (0°C) solution of 2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propionaldehyde (2.0g, 7.08mmol) in ethanol (30ml), and the mixture stirred at 0°C for 1 hour. After quenching with water (55ml), the reaction mixture is extracted with diethyl ether (3 x 25ml). The combined organic extracts are washed with water, brine, then dried (Na_2SO_4) and concentrated to a solid which is purified by silica flash chromatography (20:1 hexanes:ethyl

acetate to 3:1 hexanes:ethyl acetate) to provide the title compound as a racemic solid. MS: m/z (M+1) 285.

Preparation 31

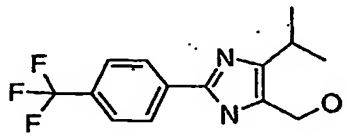
2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-2-ol



To a cooled (0°C) solution of 1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethanone (1.0g, 3.72mmol) in tetrahydrofuran (10ml) is added methylmagnesium bromide (3M in diethyl ether)(1.9ml, 5.6mmol) dropwise over 3 minutes. After stirring at 0°C for 90 minutes, the mixture is adjusted to pH 6 with 1N HCl, and then diluted with diethyl ether (30ml) and water (40ml). The organic layer is removed and the remaining aqueous layer extracted with diethyl ether (2 x 25ml). The combined organic extracts are combined and washed with water, brine, dried (Na_2SO_4), and concentrated to an oil. Purification by silica chromatography (20:1 hexanes:ethyl acetate to 4:1 hexanes:ethyl acetate) provided the title compound as an oil. MS: m/z (M+1) 285.

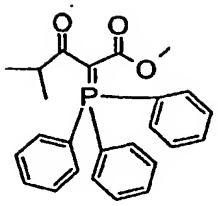
Preparation 32

[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-yl]-methanol



Step A

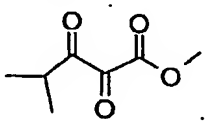
4-Methyl-3-oxo-2-(triphenyl-15-phosphanylidene)-pentanoic acid methyl ester



To a solution of isobutric acid (4.4 g, 50 mmol) and (triphenyl-15-phosphanylidene)-acetic acid methyl ester (16.7 g, 50 mmol)in methylene chloride (500 mL) is added DMAP (610 mg, 5 mmol) and EDCI (9.6 g, 50 mmol) at 0~5 °C, then warmed to room temperature. The reaction mixture is quenched by 1N NaOH, layers are separated, the organic layer is washed with water and brine, dried over sodium sulfate. Concentration yields the title compound.

Step B

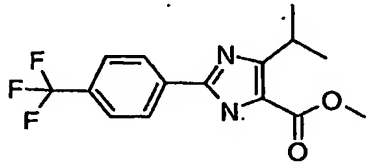
4-Methyl-2,3-dioxo-pentanoic acid methyl ester



To a solution of 4-Methyl-3-oxo-2-(triphenyl-15-phosphanylidene)-pentanoic acid methyl ester (2.0 g, 4.95 mmol) in methylene chloride is bubbled ozone for 30 min at -78 °C, then the reaction mixture is loaded on silica gel column, eluted with hexanes and ethyl acetate giving 0.51 g of the title compound.

Step C

5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid methyl ester

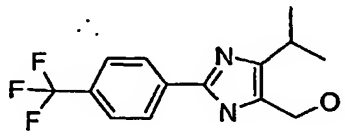


To a slurry of NH4OAc (2.48 g) in acetic acid is added 4-Methyl-2,3-dioxo-pentanoic acid methyl ester (0.51 g, 3.22 mmol) and 4-Trifluoromethyl-benzaldehyde (1.11g). The

mixture is heated at 60 oC for 1h, acetic acid is evaporated. The residue is dissolved in ethyl acetate, washed with NaHCO3, water and brine, dried over sodium sulfate. Concentration and column chromatography on silica gel yields the title compound (0.5 g).

Step D

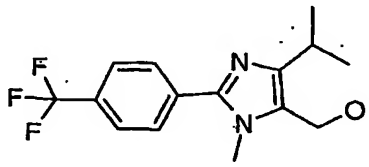
[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-yl]-methanol



A THF (5 mL) solution of 5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid methyl ester (0.47 g, 1.51 mmol) is cooled to 0 °C and a 1M $LiAlH_4$ (1.51 mL, 1.51 mmol) is added slowly. The reaction is warmed to room temperature slowly, after stirring at room temperature for 2 h, tlc (15% EtOAc/hexane) showed that all the starting ester had been consumed. The reaction is cooled and carefully quenched with water, 5N NaOH. The light tan solid is filter through celite and dried to give 0.4 g of the title compound.

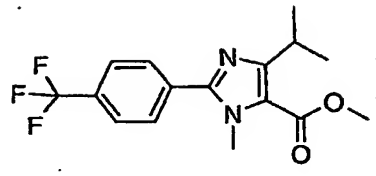
Preparation 33

[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-yl]-methanol



Step A

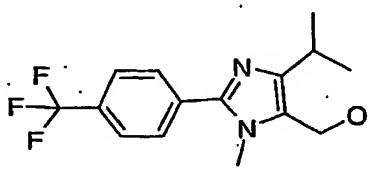
5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid methyl ester



To a solution of 5-isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid methyl ester (3.0 g, 9.6 mmol) in DMF (100 mL) is added sodium hydride (60 %, 0.58 g) at 0~5 °C. The mixture is stirred at 0~5 °C for 30 min, methyl iodide (1.2 mL) is added. The reaction mixture is warmed to room temperature and stirred overnight, wuenched by water, extracted with ethyl acetate, dried over sodium sulfate. Concentration yields the title compound (2.5 g).

Step B

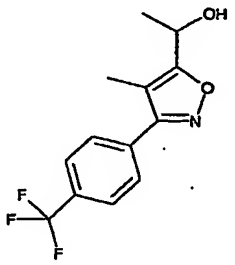
[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-yl]-methanol



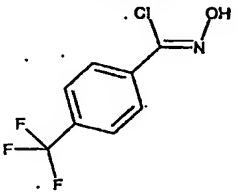
THF (10 mL) solution of 5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazole-4-carboxylic acid methyl ester(2.36 g, 7.23 mmol) is cooled to 0 °C and a 1M $LiAlH_4$ (7.5 mL, 7.5 mmol) is added slowly. The reaction is warmed to room temperature slowly, after stirring at room temperature for 2 h, tlc (15% EtOAc/hexane) showed that all the starting ester had been consumed. The reaction is cooled and carefully quenched with water, 5N NaOH. The light tan solid is filter through celite and dried to give 1.9 g of the title compound.

Preparation 34

1-[4-Methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethanol



Step A

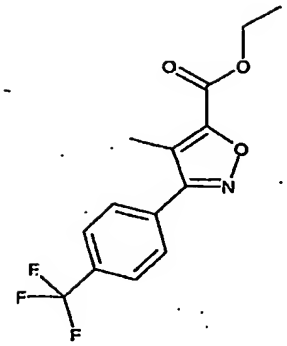


4-Trifluoromethyl-benzaldehyde (3.48 g, 20.0 mmol) in EtOH (50 mL) is added NH_2OH-HCl (1.53 g, 22.0 mmol). The mixture is stirred and heated to reflux at 84 °C for 2 hours. It is then cooled down and concentrated and purified on silica gel chromatography column with 10-20% EtOAc/Hexanes to obtain the oxime intermediate.

The oxime intermediate (2.40 g, 12.7 mmol) is then dissolved in DMF (10 mL) and added the NCS (0.93 g, 6.95 mmol). Use heat gun to initiate the reaction and then add another portion of NCS (0.93 g, 6.95 mmol). The reaction mixture is stirred at room temperature for 2 hours and quenched with water (50 mL). The mixture is extracted with EtOAc (50 mL x2) and the combined organics are dried (Na_2SO_4), concentrated, and purified on silica gel chromatography column with 20-50% EtOAc/Hexanes to yield the title compound (2.60 g, 92%).

Step B

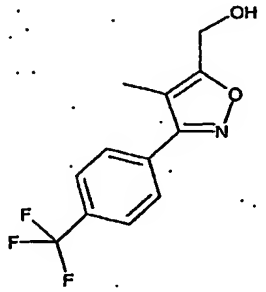
4-Methyl-3-(4-trifluoromethyl-phenyl)-isoxazole-5-carboxylic acid ethyl ester



To a solution of N-Hydroxyl-4-trifluoromethyl-benzimidoyl chloride (0.65 g, 2.91 mmol) and but-2-ynoic acid ethyl ester (0.49 g, 4.36 mmol) in EtOAc (3.0 mL) is added Et_3N dropwisely while stirred vigorously. The resulted suspension is heated to 80 °C for 12 hours. It is then filtered and the filtrate is purified on silica gel chromatography column with 10-15% EtOAc/Hexanes to obtain the product (410 mg, 47%).

Step C

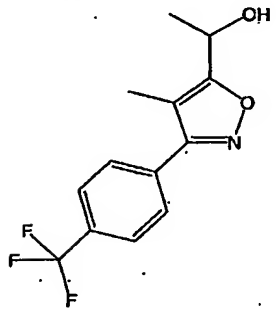
[4-Methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-methanol



A solution of 4-methyl-3-(4-trifluoromethyl-phenyl) isoxazole-5-carboxylic acid ethyl ester (810 mg, 2.71 mmol) in THF (30 mL) is treated with $LiBH_4$ (295 mg, 13.5 mmol). The suspension is stirred at room temperature for 48 hours and then quenched water (20 mL). The mixture is extracted with EtOAc (50 mL x2) and the combined organics are dried (Na_2SO_4), concentrated, and purified on silica gel chromatography column with 50% EtOAc/Hexanes to yield the title compound (480 mg g, 69%).

Step D

1-[4-Methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethanol

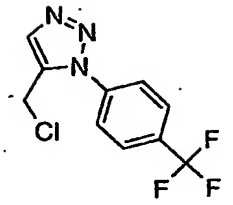


A solution of [4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-methanol (251 mg, 0.976 mmol) is treated with MnO_2 (168 mg, 1.95 mmol) and the suspension is stirred at 75 °C for 24 hours. The mixture is filtered and purified on silica gel chromatography column with 25% EtOAc/Hexanes to yield the aldehyde intermediate (165 mg).

A solution of that aldehyde intermediate (165 mg, 0.647 mmol) in THF (10 mL) at -78 °C is treated with MeMgBr (0.43 mL, 3.0 M). The mixture is stirred while warmed up to room temperature over 60 minutes. The reaction is then quenched with water (1.0 mL) and HCl (5 mL, 0.1 N). The mixture is extracted with EtOAc (50 mL x2) and the combined organics are dried (Na_2SO_4), concentrated, and purified on silica gel chromatography column with 30% EtOAc/Hexanes to yield the title compound (160 mg, 91%).

Preparation 35

5-Chloromethyl-1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazole



Step A

To a slurry of (4-Trifluoromethyl-phenyl)-hydrazine (1.8 g, 10.22 mmol) in water (50 mL) at 0°C under nitrogen is slowly added concentrated hydrochloric acid (14 mL). In a separate round bottom flask, sodium nitrite (2.0 g, 34 mmol) is dissolved in water (10 mL) and transferred to the reaction slurry slowly by pipette. The mixture is allowed to stir at 0°C open to air and monitored by TLC. Upon complete consumtion of starting material, the reaction is diluted with ethyl acetate and the two phases are seperated. The organic layer is washed, dried, filtered and concentrated. The crude 1-azido-4-trifluoromethyl-benzene is used immediately without further purification.

Step B

1-azido-4-trifluoromethyl-benzene (10.22 mmol) is dissolved in anhydrous dimethyl formamide (4 mL) and methylpropriolate (3.6 mL, 40 mmol) is added with stirring under nitrogen at room temperature. The reaction is heated to 45°C and monitored by TLC. After the starting material is completely consumed, the reaction is cooled to room temperature and concentrated. The reaction is diluted with chloroform and washed with water and brine, dried over sodium sulfate, then concentrated. The residue is further purified using flash column chromatography. The regioisomers 3-(4-Trifluoromethyl-phenyl)-3H-[1,2,3]triazole-4-carboxylic acid methyl ester (0.074g, 0.2731 mmol), 4% yield, and 1-(4-Trifluoromethyl-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid methyl ester (0.510g, 1.88 mmol), 18% yield, are formed in roughly a 1:4 ratio.

Step C

1-(4-Trifluoromethyl-phenyl)-1H-[1,2,3]triazole-4-carboxylic acid methyl ester (0.510g, 1.88 mmol) is dissolved into

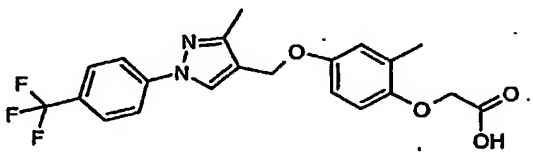
anhydrous tetrahydrofuran (10 mL) and cooled to 0°C under nitrogen. A solution of lithium aluminum hydride, 1.0M in THF, (1.90 mL, 1.90 mmol) is slowly added and the reaction is monitored by TLC. Upon complete consumtion of starting material, the reaction is quenched with water, 20% sodium hydroxide, and water additions, diluted with diethyl ether, followed by filtration through a celite plug. The two phases are seperated. The organic layer is washed, dried, filtered and concentrated. The crude [1-(4-Trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-yl]-methanol (0.314 g, 1.29 mmol), 69% yield, is used without further purification.

Step D

[1-(4-Trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-yl]-methanol (0.314 g, 1.29 mmol), is dissolved into anhydrous dichloromethane (5 mL) and cooled to 0°C under nitrogen. Triethyl amine (0.360 mL, 2.58 mmol) and methane sulfonyl chloride (0.150 mL, 1.94 mmol) are then slowly added and the reaction is monitored by TLC. Upon complete consumtion of starting material, the reaction is diluted with dichloromethane and extracted against saturated sodium bicarbonate solution. The organic layer is washed with water and brine, then dried over anhydrous sodium sulfate, and concentrated. The crude 4-Chloromethyl-1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazole (0.337 g, 1.29 mmol), 100% yield, is used without further purification.

Example 1

{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid



Step A

4-Chloromethyl-3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole

To a cooled (0°C) solution of [3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol (333mg, 1.29mmol) and triethylamine (0.36ml, 2.58mmol) in dichloromethane (5ml) is added methanesulfonyl chloride (0.16ml, 2.06mmol) dropwise over 5 minutes. After stirring at 0°C for 2 hours, the mixture is diluted with dichloromethane (15ml) and washed with saturated aqueous sodium bicarbonate (2 x 15ml). The organic layer is washed with water, brine, dried (Na_2SO_4), and concentrated to the title compound as a solid and is used without further purification. MS: m/z (M+1) 275.

Step B

{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid methyl ester

To a solution of (4-Hydroxy-2-methyl-phenoxy)-acetic acid methyl ester (99.3mg, 0.50mmol) and 4-Chloromethyl-3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole (167mg, 0.61mmol) in acetonitrile (1.5ml) is added cesium carbonate (260mg, 0.80mmol) and the resulting suspension stirred at ambient temperature for 18 hours. Filtration of the mixture and concentration of the filtrate yields a solid which is purified by silica chromatography (15:1 hexanes:ethyl acetate to 5:1 hexanes:ethyl acetate) to provide the title compound as a white solid. MS: m/z (M+1) 435

Step C

{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid

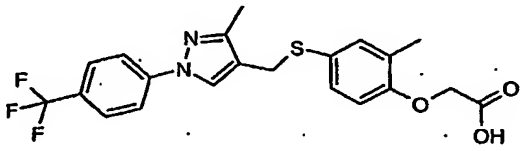
A solution of {2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid methyl ester (120mg, 0.27mmol) in methanol (10ml) is treated with 5N NaOH (0.54ml, 2.7 mmol), and the solution is stirred at ambient temperature for 24 hours. The mixture is concentrated to dryness to give a solid which is dissolved

in water (10ml) and ethyl acetate (15ml), and the solution is then adjusted to pH 3 with 6N HCl. After extraction of the aqueous layer with ethyl acetate (2 x 15ml), the organic extracts are combined and washed with water, brine, then dried (Na_2SO_4) and concentrated to provide the title compound as a white solid. MS: m/z (M+1) 421. The structure is also confirmed by proton NMR.

The following compound is prepared according to the procedure outlined above in Example 1:

Example 2

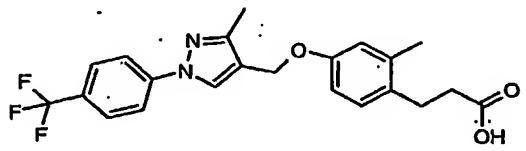
{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS: m/z (M+1) 437: The structure is also confirmed by proton NMR.

Example 3

3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid



Step A

3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid methyl ester

To a cooled (0°C) solution of [3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-methanol (135mg, 0.52mmol) and 3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester (123mg, 0.63mmol) in tetrahydrofuran (5.0ml) is

added tri-n-butylphosphine (0.195ml, 0.78mmol) followed by addition of 1,1'-(azodicarbonyl)dipiperidine (197mg, 0.78mmol) portion-wise over 3 minutes. The mixture is stirred at 0°C for 10 minutes, then removed from the cold bath and stirred for 18 hours. The mixture is diluted with hexanes (10ml), filtered to remove insolubles, and the filtrate concentrated to an oil which is purified by silica flash chromatography (35:1 hexanes:ethyl acetate to 5:1 hexanes:ethyl acetate) to provide the title compound as a colorless oil. MS: m/z (M+1) 433.

Step B

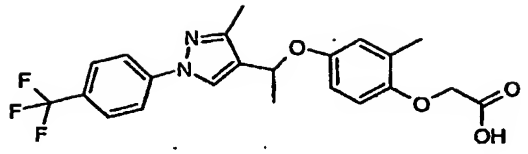
3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid

A solution of 3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid methyl ester (98mg, 0.22mmol) in methanol (3ml) is treated with 5N NaOH (0.11ml, 0.56 mmol), and the solution is stirred at ambient temperature for 18 hours. The mixture is concentrated to dryness to give a solid, which is dissolved in water (10ml) and ethyl acetate (15ml), and the resulting solution is then adjusted to pH 3 with 6N HCl. After extraction of the aqueous layer with ethyl acetate (2 x 15ml), the organic extracts are combined and washed with water, brine, then dried (Na_2SO_4) and concentrated to provide the title compound as a white solid. MS: m/z (M+1) 419. The structure is also confirmed by proton NMR.

The following compounds are prepared according to the procedure outlined above in Example 3:

Example 4

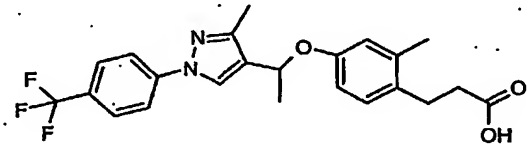
(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenoxy)-acetic acid



MS: m/z (M+1) 435. The structure is also confirmed by proton NMR.

Example 5

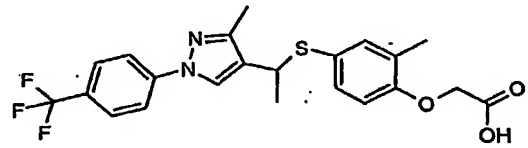
(R,S)-3-{2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-propionic acid



MS: m/z (M+1) 433. The structure is also confirmed by proton NMR.

Example 6

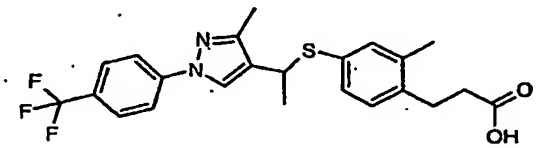
(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid



MS: m/z (M+1) 451. The structure is also confirmed by proton NMR.

Example 7

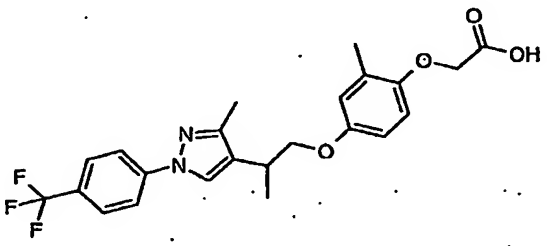
(R,S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid



MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 8

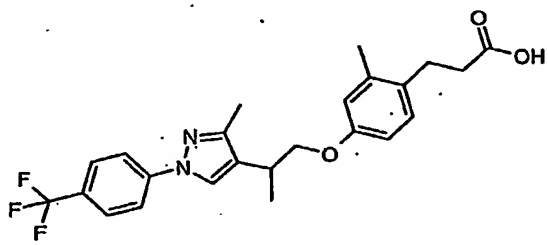
(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid



MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 9

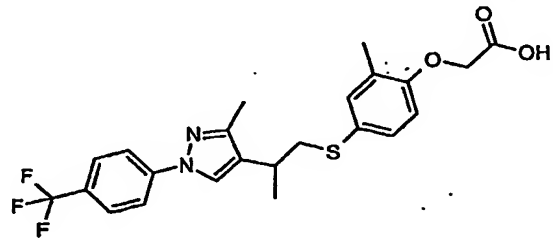
(R,S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



MS: m/z (M+1) 447. The structure is also confirmed by proton NMR.

Example 10

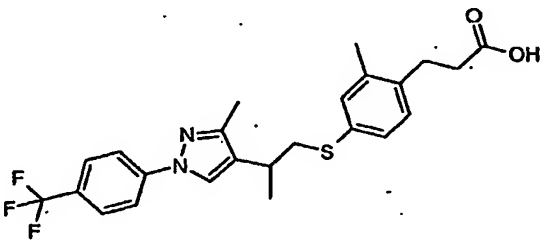
(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 11

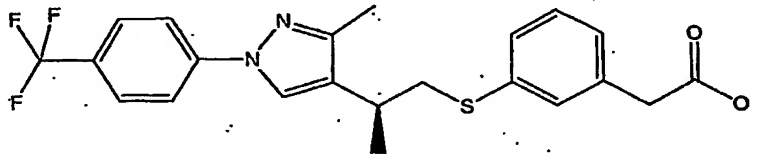
(R,S)-3-{2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid



MS: m/z (M+1) 463. The structure is also confirmed by proton NMR.

Example 12

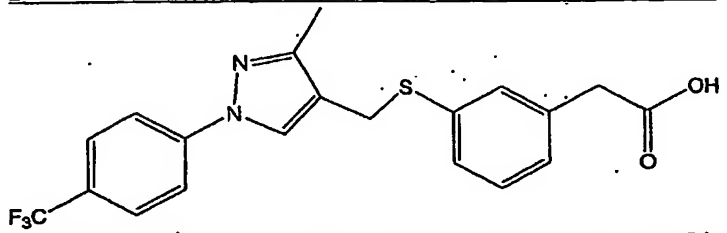
{3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-acetic acid



MS (ES): 435 (M^++1). The structure is confirmed by ^1H NMR spectroscopy.

Example 13

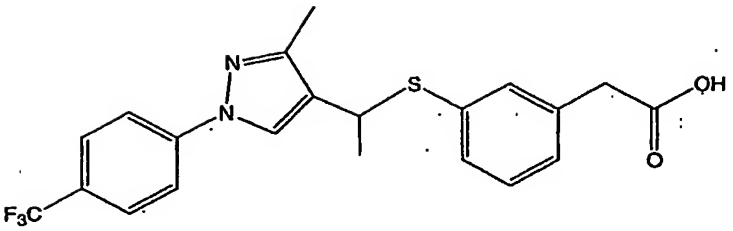
{3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenyl}-acetic acid



MS (ES): 407 (M^++1). The structure is confirmed by ^1H NMR spectroscopy.

Example 14

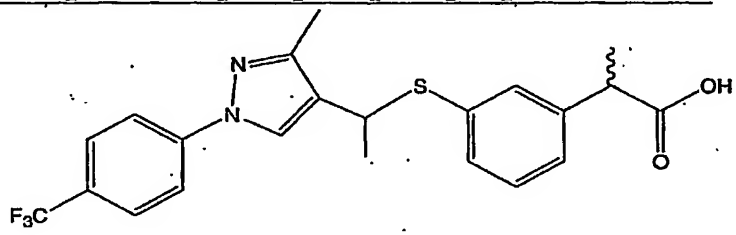
(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-acetic acid



MS (ES): 421 (M^++1). The structure is confirmed by ^{1}H NMR spectroscopy.

Example 15

2-(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid



Step A

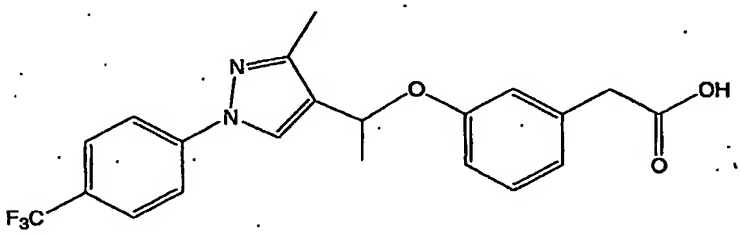
Lithium hexamethyldisilazane (0.51 mL, 0.51 mmol) is added dropwise to a solution of(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-acetic acid methyl ester (0.20 g, 0.46 mmol) in 5 mL THF at -78 C. The resultant solution is stirred for 30 minutes and methyl iodide (0.034 mL, 0.55 mmol) is added dropwise. The solution is allowed to warm to room temperature over two hours and stirred overnight upon which it is poured into an aqueous solution of NH4Cl. The aqueous layer is extracted with ethyl acetate (3x25mL) and washed with water (25 mL) and brine (25mL). Chromatography (10% ethyl acetate/hexane) provided the ester.

Step B

The ester is hydrolyzed in a similar fashion providing the titled compound. MS (ES) 435 (M^++1). The structure is confirmed by ^{1}H NMR spectroscopy.

Example 16

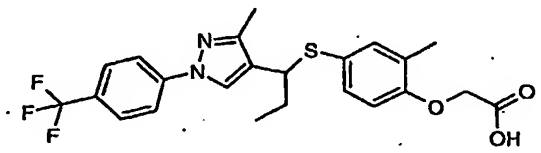
(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-acetic acid



MS (ES): 405 (M^++1). The structure is confirmed by 1H NMR spectroscopy.

Example 17

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



Step A

(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid ethyl ester

Zinc iodide (105mg, 0.33mmol) is added to a solution of 1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propan-1-ol (185mg, 0.65mmol) and (4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (176mg, 0.78mmol) in 1,2-dichloroethane (1ml) and the solution stirred at ambient temperature for 1 hour. The mixture is diluted with water (20ml) and dichloromethane (10ml), the organic layer is removed, and the remaining aqueous layer extracted with dichloromethane (2 x 10ml). The combined organic extracts

are combined and washed with brine, then dried (Na_2SO_4) and concentrated to an oil which is purified by silica chromatography (15:1 hexanes:ethyl acetate to 10:1 hexanes:ethyl acetate) to give the title compound as a colorless oil. MS: m/z (M+1) 493.

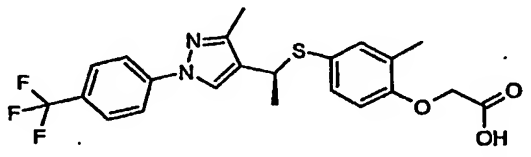
Step B

(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid

A solution of (2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid ethyl ester (239mg, 0.48mmol) in methanol (4ml) is treated with 2N NaOH (0.72ml, 1.44 mmol), and the solution is stirred at ambient temperature for 16 hours. The mixture is concentrated to dryness to give a solid, which is dissolved in water (15ml) and ethyl acetate (15ml), and the resulting solution is then adjusted to pH 3 with 6N HCl. After extraction of the aqueous layer with ethyl acetate (2 x 20ml), the organic extracts are combined and washed with water, brine, then dried (Na_2SO_4) and concentrated to provide the title compound as a white solid. MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 18

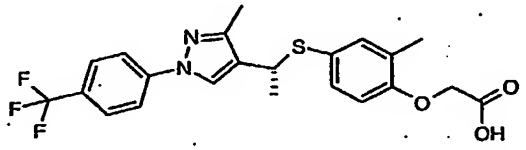
(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralcel OD (4.6 x 250mm) column with an eluent consisting of 10% n-propanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 451. The structure is also confirmed by proton NMR.

Example 19

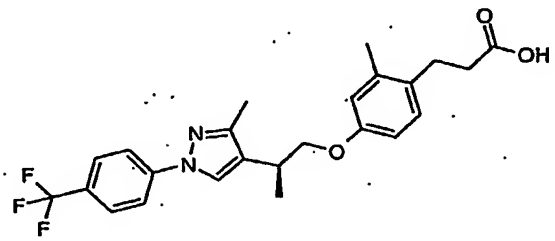
(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralcel OD (4.6 x 250mm) column with an eluent consisting of 10% n-propanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 451. The structure is also confirmed by proton NMR.

Example 20

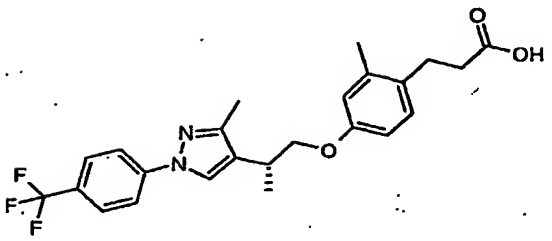
(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 447. The structure is also confirmed by proton NMR.

Example 21

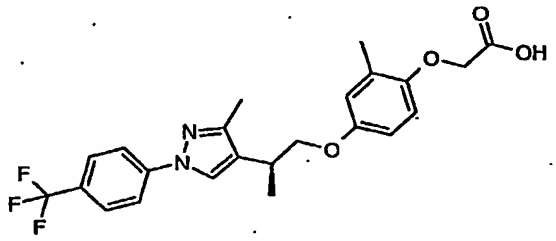
(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 447. The structure is also confirmed by proton NMR.

Example 22

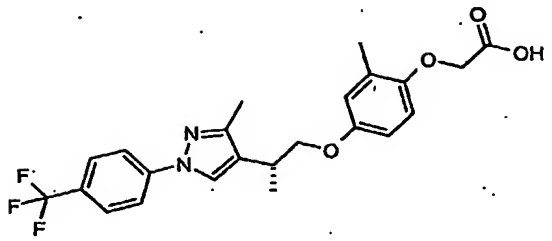
(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 23

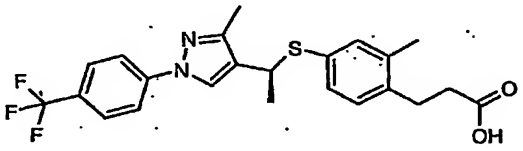
(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 24

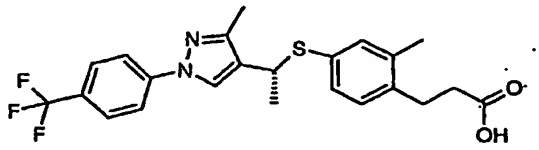
(S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 25

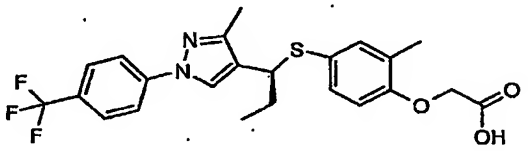
(R)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 20% isopropanol in heptane containing 0.2% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 449. The structure is also confirmed by proton NMR.

Example 26

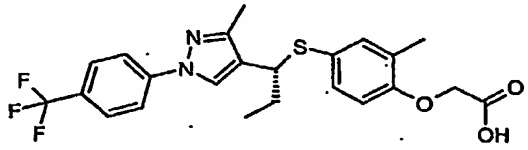
(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 10% ethanol in heptane containing 0.1% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 27

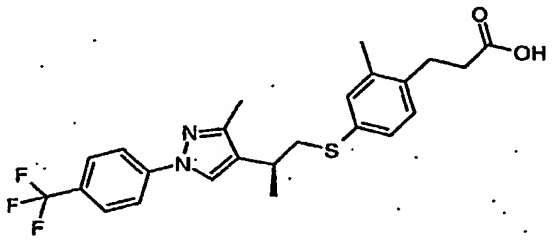
(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 10% ethanol in heptane containing 0.1% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 28

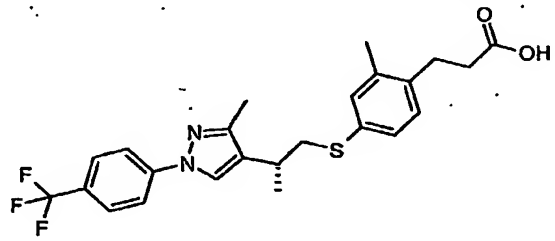
(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 15% ethanol in heptane containing 0.1% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 463. The structure is also confirmed by proton NMR.

Example 29

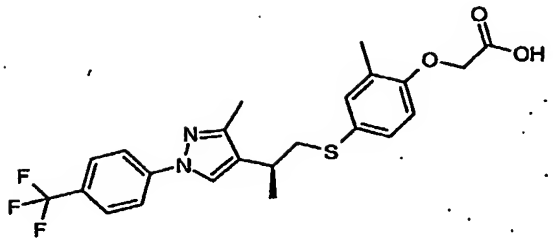
(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralpak AD (4.6 x 250mm) column with an eluent consisting of 15% ethanol in heptane containing 0.1% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 463. The structure is also confirmed by proton NMR.

Example 30

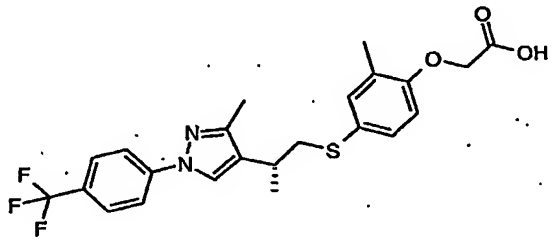
(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralcel OJ (4.6 x 250mm) column with an eluent consisting of 100% ethanol containing 0.2% trifluoroacetic acid as buffer, and eluted as the first enantiomer. MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 31

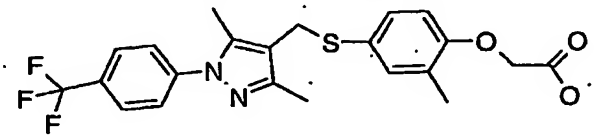
(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid



The title compound is obtained via chiral chromatography of the racemate on a Chiralcel OJ (4.6 x 250mm) column with an eluent consisting of 100% ethanol containing 0.2% trifluoroacetic acid as buffer, and eluted as the second enantiomer. MS: m/z (M+1) 465. The structure is also confirmed by proton NMR.

Example 32

{4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



Step A

{4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester

To a solution of 4-Chloromethyl-3,5-dimethyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazole (172 mg, 0.6 mmol) and (4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (152 mg, 0.67 mmol) in acetonitrile (2.5 mL) is added Ca_2CO_3 (325 mg, 1 mmol). The mixture is stirred at room temperature over night, quenched by water, extracted with ethyl acetate, dried over sodium sulfate. Concentration yields the crude product.

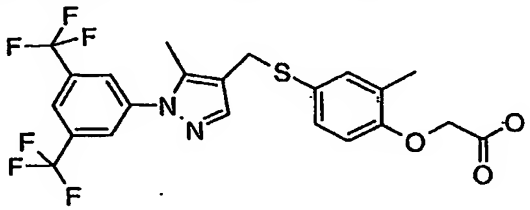
Step B

{4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid

To a solution of {4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester from step A in THF (1 mL is added LiOH (1.0 M, 1 mL). It is stirred at room temperature for 2hrs, is acidified with 5 N HCl, extracted with ether, dried over sodium sulfate. Concentration and reversed phase HPLC purification (acetone/water/TFA as eluent) yields the title compound (62 mg). MS (ES): 453(M^++1); the structure is also confirmed by ^1H NMR.

Example 33

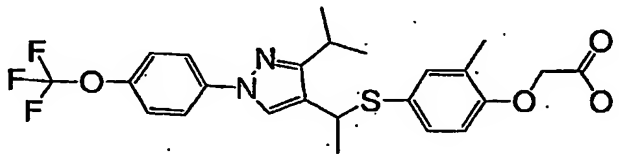
{4-[1-(3,5-Bis-trifluoromethyl-phenyl)-5-methyl-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



MS (ES): 505.1(M^++1); the structure is also confirmed by ^1H NMR.

Example 34

(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid



Step A

(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester

To a solution of 1-[3-Methyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethanol (314 mg, 1 mmol) in 1,2-dichloroethane (4 mL) is added ZnI_2 (160 mg, 0.5 mmol), followed by addition of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (270 mg, 0.1.2 mmol). After 2hrs, the reaction mixture is loaded on silica gel column directly and eluted with hexanes/ethyl acetate giving the title compound (498 mg).

Step B

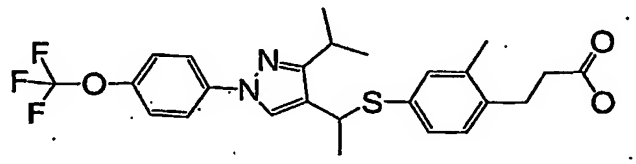
(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid

To a solution of (4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid ethyl ester (110 mg) from step A in ethanol (1 mL is added NaOH (5.0 M, 1 mL). After stirring at 50 °C for 2hrs, it is acidified with 5 N HCl, extracted with ether, dried over sodium sulfate. Concentration and reversed phase HPLC purification (acetone/water/TFA as eluent) yields the title compound (86 mg). MS (ES): 493.3(M^+-1).

The following compounds are made in a similar manner:

Example 35

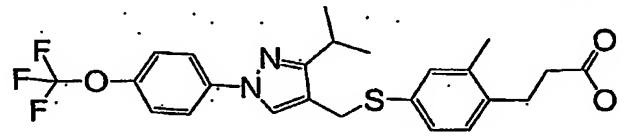
3-{4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenyl}-propionic acid



MS (ES): 491.3(M^+-1).

Example 36

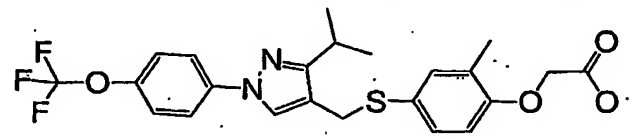
3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid



MS (ES): 479.1(M^++1).

Example 37

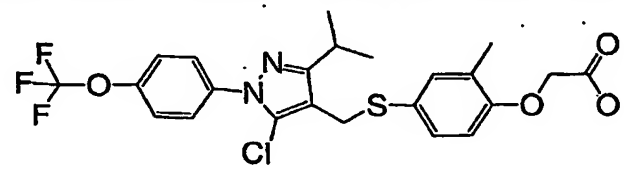
{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



MS (ES): 481.1(M^++1).

Example 38

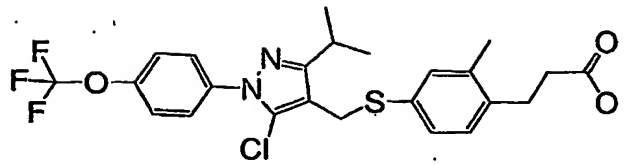
{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



MS (ES): 513.1(M^++1, ^{37}Cl).

Example 39

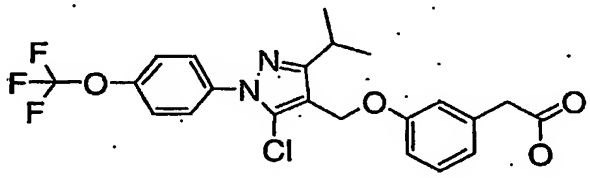
3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid



MS (ES): 515.1(M^++1, ^{37}Cl).

Example 40

{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid



Step A

{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid ethyl ester

A solution of [5-chloro-1-(4-difluoromethoxy-phenyl)-3-isopropyl-1H-pyrazol-4-yl]-methanol (100 mg, 0.3 mmol) in toluene (3.0 mL) is degassed and filled with nitrogen for 3 times. 1,1'-(Azodicarbonyl)-dipiperidine (120mg, 0.5 mmol) is added to the reaction mixture under nitrogen at 0 °C, followed by the addition of tributylphosphine (0.124 mL, 0.5 mmol) and (3-hydroxy-phenyl)-acetic acid (83 mg, 0.5 mmol). The reaction mixture is allowed to warm to room temperature and stirred overnight, the mixture is loaded on silica gel column. Chromatography yields the title compound (120 mg).

Step B

{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid

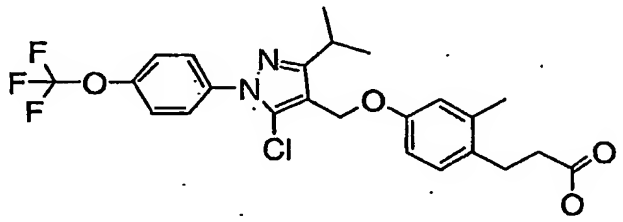
{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid ethyl ester (120 m) from step A is taken into ethanol (1 mL) and treated with NaOH (5.0 N, 1 mL) at 50 °C for 2hrs. The reaction mixture is acidified with 5 N HCl, extracted with ethyl ether, dried

over sodium sulfate. Concentration yields the title compound (120 mg). MS (ES): 469.1(M^+-1), the structure is also confirmed by proton NMR.

The following compounds are made in a similar manner:

Example 41

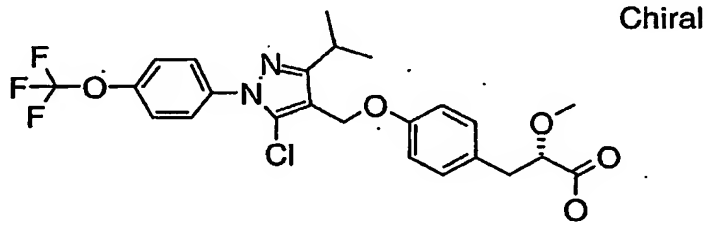
3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid



MS (ES): 497.1(M^++1), the structure is also confirmed by proton NMR.

Example 42

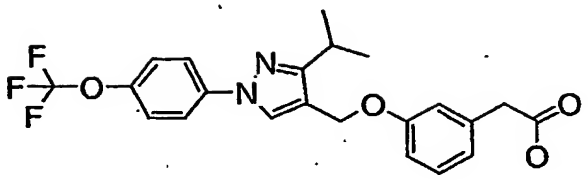
(S)-3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-2-methoxy-propionic acid



MS (ES): 513.1(M^++1), the structure is also confirmed by proton NMR.

Example 43

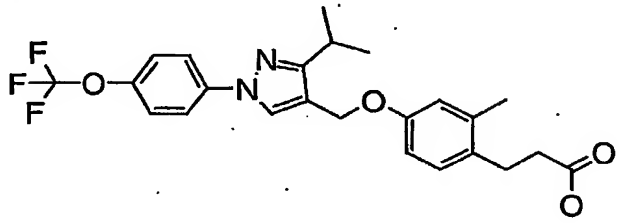
{3-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid



MS (ES): 435.5(M^++1), the structure is also confirmed by proton NMR.

Example 44

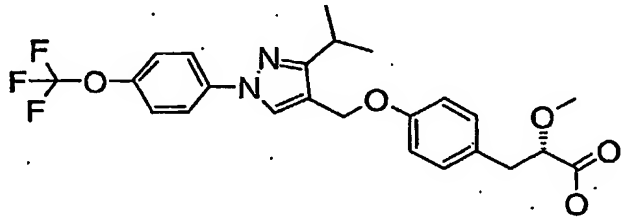
3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxyl-2-methyl-phenyl}-propionic acid



MS (ES): 463.4(M^++1), the structure is also confirmed by proton NMR.

Example 45

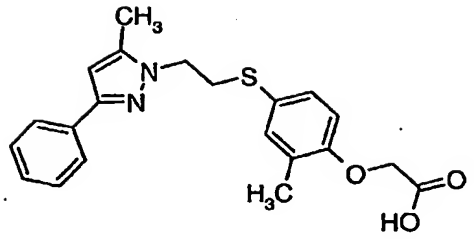
3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxyl-phenyl}-2-methoxy-propionic acid



MS (ES): 479.5(M^++1), the structure is also confirmed by proton NMR.

Example 46

{2-Methyl-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid



Step 1

(4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (113 mg, 0.500 mmol) is dissolved into anhydrous acetonitrile(ACN) (2 mL). Toluene-4-sulfonic acid 2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethyl ester (176 mg, 0.495 mmol) is added to the reaction, followed by the addition of cesium carbonate (326 mg, 1.00 mmol). The reaction is allowed to stir under nitrogen at room temperature and monitored by TLC and HPLC. Upon complete consumption of the tosylate, the reaction is diluted with diethyl ether and quenched with 0.1N NaOH. The two phases are separated, then the organic layer washed with water and brine. The organic phase is dried over anhydrous sodium sulfate and concentrated under vacuum. The residue is further purified using either EtOAc/Hexanes(1:9) or Acetone/Hexanes(1:9) gradients on silica gel chromatography to yield {2-Methyl-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid ethyl ester (133 mg, 0.346 mmol) or 70%.

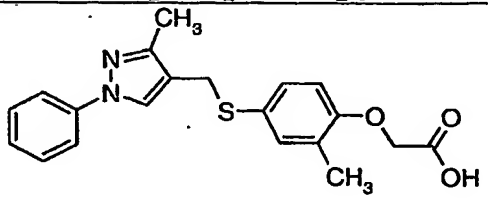
Step 2

{2-Methyl-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid ethyl ester (133 mg, 0.346 mmol) is dissolved in tetrahydrofuran (1mL) and 1N LiOH (1mL) is added. The mixture is heated to reflux until the conversion is complete. Upon complete conversion, the reaction is cooled to room temperature and 1N HCl (1mL) is added. The mixture is diluted with diethyl ether and extracted with 1N HCl. The organic layer is washed with water and brine, then dried over anhydrous sodium sulfate. Concentration of the solvent reveals the pure {2-Methyl-4-

[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid in near quantitative yield (130 mg, 0.340 mmol).

Example 47

[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid



Step 1

(4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (113 mg, 0.500 mmol) is dissolved into anhydrous acetonitrile(ACN) (2 mL). Cesium carbonate (326 mg, 1.00 mmol) is added to the reaction, followed by the addition of 4-Chloromethyl-5-methyl-1-phenyl-1H-pyrazole (102 mg, 0.495 mmol). The reaction is allowed to stir under nitrogen at room temperature and monitored by TLC and HPLC. Upon complete consumption of the chloride, the reaction is diluted with diethyl ether and quenched with 0.1N NaOH. The two phases are separated, then the organic layer washed with water and brine. The organic phase is dried over anhydrous sodium sulfate and concentrated under vacuum. The residue is further purified using either EtOAc/Hexanes(1:9) or Acetone/Hexanes(1:9) gradients on silica gel chromatography to yield [2-Methyl-4-(5-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid ethyl ester (157 mg, 0.396 mmol) or 80%.

Step 2

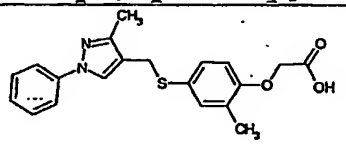
[2-Methyl-4-(5-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid ethyl ester (157 mg, 0.396 mmol) is dissolved in tetrahydrofuran (1mL) and 1N LiOH (1mL) is added. The mixture is heated to reflux until the conversion is complete. Upon complete conversion, the reaction is cooled to room temperature and 1N HCl (1mL) is added. The mixture is diluted with diethyl ether and

extracted with 1N HCl. The organic layer is washed with water and brine, then dried over anhydrous sodium sulfate. Concentration of the solvent reveals the pure [2-Methyl-4-(5-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid in near quantitative yield (138 mg, 0.375 mmol).

The following compounds are made in a substantially similar manner:

Example 48

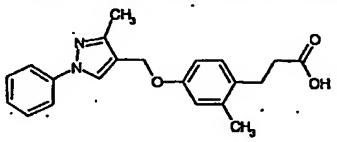
[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid



MS (ES): 351.13(M^++H).

Example 49

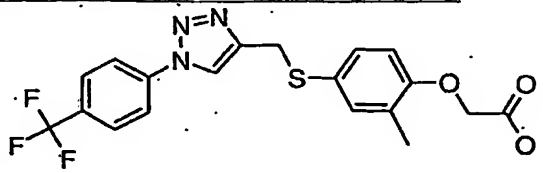
3-[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethoxy)-phenyl]-propionic acid



MS (ES): 369.04(M^++H).

Example 50

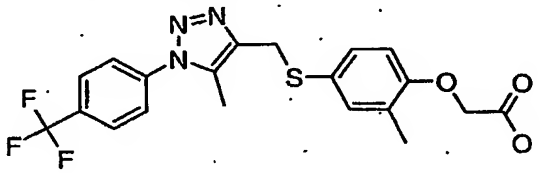
{2-Methyl-4-[1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 424.4(M^++H).

Example 51

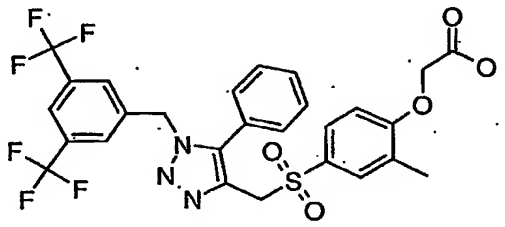
{2-Methyl-4-[5-methyl-1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 438.4(M^++H).

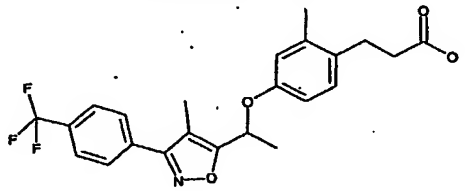
Example 52

{4-[1-(3,5-Bis-trifluoromethyl-benzyl)-5-phenyl-1H-[1,2,3]triazol-4-ylmethanesulfonyl]-2-methyl-phenoxy}-acetic acid



MS (ES): 614.5(M^++H).

Example 53



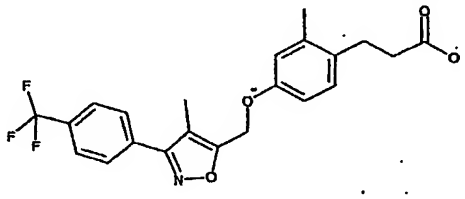
3-(2-Methyl-4-{1-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethoxy}-phenyl)-propionic acid

A solution of 3-(4-hydroxy-2-methyl-phenyl)-propionic acid methyl ester (88 mg, 0.45 mmol) and 1-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethanol (81 mg, 0.30 mmol) in toluene (10 mL) is degassed and filled with nitrogen for 3 times. Tributylphosphine (91 mg, 0.45 mmol) is added to the reaction mixture under nitrogen at 0 °C, followed by addition of of 1,1'-(azodicarbonyl)-dipiperidine (88 mg, 0.45 mmol). The reaction mixture is allowed to warm

to room temperature and stirred for 48 hours. The mixture is loaded directly on silica gel chromatography with 25% EtOAc/Hexanes to obtain the intermediate ester. This intermediate is taken into THF (0.5 mL) and MeOH 1.0 mL), and is treated with NaOH (2.0 N, 1.5 mL) for 2 hours. The reaction mixture is acidified with 5 N HCl, extracted with ethyl ether, dried over sodium sulfate. Concentration yields the title compound (21 mg, 16%). MS (ES): 434.3; the structure is also confirmed by proton NMR.

Example 54

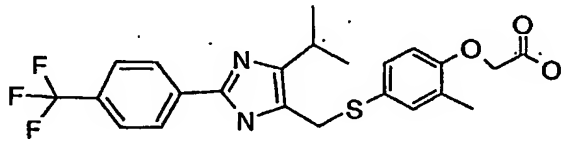
3-{2-Methyl-4-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-ylmethoxy]-phenyl}-propionic acid



MS (ES): 420.2; the structure is also confirmed by proton NMR.

Example 55

{4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



Step A

{4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester

A solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (120 mg, 0.53 mmol) and [5-isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-yl]-methanol (100 mg, 0.35 mmol) in toluene (3.0 mL) is degassed and filled with

nitrogen for 3 times. Tributylphosphine (0.13 mL) is added to the reaction mixture under nitrogen at 0 °C, followed by addition of of 1,1'-(azodicarbonyl)-dipiperidine (134 mg). The reaction mixture is allowed to warm to room temperature and stirred overnight, the mixture is loaded on silica gel column. Chromatography yields the title compound (120 mg).

Step B

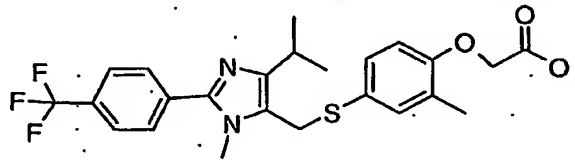
{4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid

({4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid ethyl ester (120 mg) is taken into THF (2 mL) and treated with LiOH (1.0 N, 2 mL) for 2hrs. The reaction mixture is acidified with 5 N HCl, extracted with ethyl ether, dried over sodium sulfate. Concentration yields the title compound. MS (ES): 465.2(M^++1), the structure is also confirmed by proton NMR.

The following compounds are made in a similar manner:

Example 56

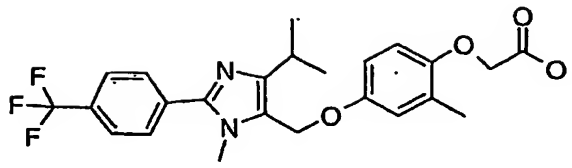
{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid



MS (ES): 477.2(M^+-1), the structure is also confirmed by proton NMR.

Example 57

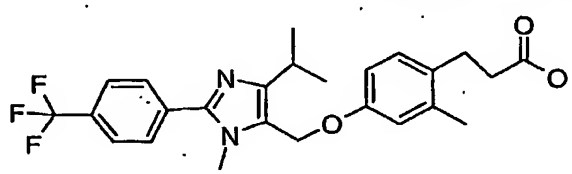
{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxyl-2-methyl-phenoxy}-acetic acid



MS (ES): 463.2(M^++1), the structure is also confirmed by proton NMR.

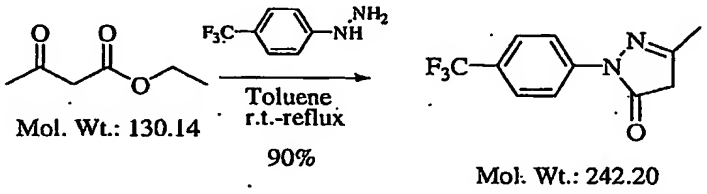
Example 58

3-{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid



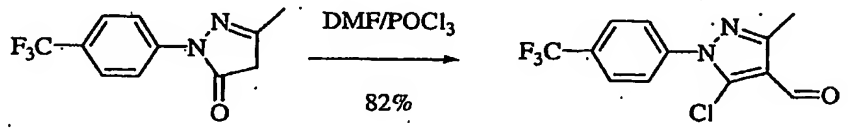
MS (ES): 461.2(M^++1), the structure is also confirmed by proton NMR.

Example 59



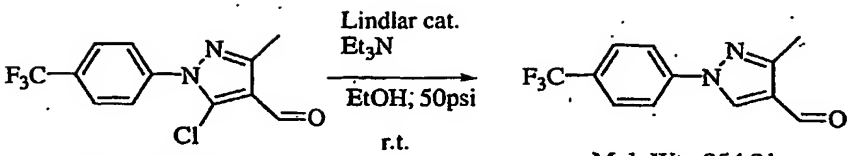
To a solution of the Trifluoromethylphenyl Hydrazine (60.4g, 0.34moles) and toluene (250.0mL) at room temperature is added ethylacetoacetate (48.09mL, 0.38m). Reaction solution is then stirred overnight at r.t. for 12 hrs (N.B. reaction generally becomes hazy after an hour of stirring). Heated at reflux with continuous azeotropic removal of water and volatile organic solvents for another 12hrs (note: the volume of toluene removed during azeotrope should be replaced during the course of the reaction). Reaction is monitored by TLC (1:1 EtoAc/Heptane). After the reaction is deemed to be complete, heptane (500.0mL) is added to the hot solution. An off tan precipitate is observed upon equilibration to ambient temperature. The tan precipitate is

filtered and the cake washed with heptane (75.0mL), dried in an oven at 50°C overnight (mass = 75.39g; 90% wt. Yield; ^1H ($CDCl_3$+ $DMSOd_6$) δ 1.82 (s, 3H), 3.16 (s, 2H), 7.22-7.25 (d, 2H, J = 8.8Hz), 7.57-7.59 (d, 1H, J = 8.8Hz), 7.66-7.68 (d, 1H, J = 8.5Hz).



Mol. Wt.: 242.20 Mol. Wt.: 288.65

To DMF (44.56mL, 0.57m) at 10°C is added $POCl_3$ (52.68mL, 0.57m) over a period of 30 minutes (caution solution solidifies after addition). To this solid is then added the pyrazolone (70.0g, 0.28m). Slowly heated mixture until dissolution is observed at 75-80°C (To aid the dissolution, an extra 40mL of DMF is added). The dark reaction solution is then heated at 90-100°C for 18hrs, after which an additional $POCl_3$ (52.6mL) is added (reaction is monitored by TLC 1:1 EtoAc/Heptane). Heating is continued for another 6hrs before the reaction mixture is very carefully reversed quenched into crushed ice over a period of 2hrs. (Extreme caution: quenching is quite exothermic and should be done very carefully. Possible induction period can be observed during quenching of excess $POCl_3$). A dark brown precipitate is observed after quenching. On equilibration to r.t., the precipitate is extracted with CH_2Cl_2 (500.0mL), washed with 2N NaOH (2X500ml), treated with Darco and anh. $MgSO_4$. Subsequent filtration over hyflo and concentration at reduced pressure on the rotovap afforded a tan precipitate (mass = 72.0g). The purity of the precipitate can be upgraded by dissolving it in a hot EtoAc (200ml), followed by a quick plug over silica gel. Concentration of the filtrate on the rotovap affords a tan solid (mass = 68.4g; 82% wt. Yield; ^1H ($CDCl_3$) δ 2.54 (s, 3H), 7.72-7.81 (m, 4H), 9.99 (s, 1H, CHO).



To Chloro/formyl starting material (520mg, 1.8mm) dissolved in EtOH (20.0mL) is added Et_3N (0.5mL) and Lindlar catalyst (0.05g). The mixture is then hydrogenated at r.t (50psi). After 2.5 hrs, ^1H nmr of an aliquot after a brief work up indicated product with no observable starting material. Reaction mixture is the filtered over hyflo, concentrated to a solid. To the solid is added CH_2Cl_2 (40.0mL) and 1NHCl (20.0mL) with stirring. Subsequent separation of lower organic layer, drying and concentrating on the rotovap afforded a tan precipitate (mass = 455mg; 100% wt.yield; ^1H ($CDCl_3$) δ 2.57 (s, 3H), 7.71-7.74 (d, 2H, J = 8.4Hz), 7.82-7.85 (d, 2H, J = 8.5Hz), 8.43 (s, 1H), 10.00 (s, 1H, CHO).

Biological Assays

Binding and Cotransfection Studies

The in vitro potency of compounds in modulating PPARα receptors are determined by the procedures detailed below. DNA-dependent binding (ABCD binding) is carried out using SPA technology with PPAR receptors. Tritium-labeled PPARα agonists are used as radioligands for generating displacement curves and IC_{50} values with compounds of the invention. Cotransfection assays are carried out in CV-1 cells. The reporter plasmid contained an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the luciferase reporter cDNA. Appropriate PPARs are constitutively expressed using plasmids containing the CMV promoter. For PPARα, interference by endogenous PPARγ in CV-1 cells is an issue. In order to eliminate such interference, a GAL4

chimeric system is used in which the DNA binding domain of the transfected PPAR is replaced by that of GAL4, and the GAL4 response element is utilized in place of the AOX PPRE. Cotransfection efficacy is determined relative to PPARα agonist reference molecules. Efficacies are determined by computer fit to a concentration-response curve, or in some cases at a single high concentration of agonist (10 μM).

These studies are carried out to evaluate the ability of compounds of the invention to bind to and/or activate various nuclear transcription factors, particularly huPPARα ("hu" indicates "human"). These studies provide in vitro data concerning efficacy and selectivity of compounds of the invention. Furthermore, binding and cotransfection data for compounds of the invention are compared with corresponding data for marketed compounds that act on huPPARα.

The binding and cotransfection efficacy values for compounds of the invention which are especially useful for modulating a PPAR receptor, are $\leq$ 100 nM and $\geq$ 50%, respectively.

Evaluation of Triglyceride Reduction and HDL Cholesterol Elevation in HuapoAI Transgenic Mice

Compounds of the present invention are studied for effects upon HDL and triglyceride levels in human apoAI mice. For each compound tested, seven to eight week old male mice, transgenic for human apoAI (C57BL/6-tgn(apoa1)1rub, Jackson Laboratory, Bar Harbor, ME) are acclimated in individual cages for two weeks with standard chow diet (Purina 5001) and water provided ad libitum. After the acclimation, mice and chow are weighed and assigned to test groups (n = 5) with randomization by body weight. Mice are dosed daily by oral gavage for 8 days

using a 29 gauge, 1-1/2 inch curved feeding needle (Popper & Sons). The vehicle for the controls, test compounds and the positive control (fenofibrate 100mg/kg) is 1% carboxymethylcellulose (w/v) with 0.25% tween 80 (w/v). All mice are dosed daily between 6 and 8 a.m. with a dosing volume of 0.2ml. Prior to termination, animals and diets are weighed and body weight change and food consumption are calculated. Three hours after last dose, mice are euthanized with CO2 and blood is removed (0.5-1.0 ml) by cardiac puncture. After sacrifice, the liver, heart, and epididymal fat pad are excised and weighed. Blood is permitted to clot and serum is separated from the blood by centrifugation.

Cholesterol and triglycerides are measured colorimetrically using commercially prepared reagents (for example, as available from Sigma #339-1000 and Roche #450061 for triglycerides and cholesterol, respectively). The procedures are modified from published work (McGowan M. W. et al., Clin Chem 29:538-542,1983; Allain C. C. et al., Clin Chem 20:470-475,1974. Commercially available standards for triglycerides and total cholesterol, respectively, commercial quality control plasma, and samples are measured in duplicate using 200 µl of reagent. An additional aliquot of sample, added to a well containing 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature on a plate shaker and absorbance is read at 500 nm and 540 nm for total cholesterol and triglycerides, respectively. Values for the positive control are always within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment are assayed at the same time to minimize inter-assay variability.

Serum lipoproteins are separated and cholesterol quantitated by fast protein liquid chromatography (FPLC) coupled to an in line detection system. Samples are applied to a Superose 6 HR size exclusion column (Amersham Pharmacia Biotech) and eluted with phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16ml/min mixed with the column effluent through a T-connection and the mixture passed through a 15 m x 0.5 mm.id knitted tubing reactor immersed in a 37 C water bath. The colored product produced in the presence of cholesterol is monitored in the flow strem at 505 nm and the analog voltage from the monitor is converted to a digital signal for collection and analysis. The change in voltage corresponding to change in cholesterol concentration is plotted vs time and the area under the curve corresponding to the elution of very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) is calculated using Perkin Elmer Turbochrome software.

Triglyceride Serum Levels in Mice Dosed with a Compound of the Invention is Compared to Mice Receiving the Vehicle to identify compounds which could be particularly useful for lowering triglycerides. Generally, triglyceride decreases of greater than or equal to 30% (thirty percent) compared to control following a 30 mg/kg dose suggests a compound that can be especially useful for lowering triglyceride levels.

The percent increase of HDLc serum levels in mice receiving a compound of the invention is compared to mice receiving vehicle to identify compounds of the invention that could be particularly useful for elevating HDL levels. Generally, and increase of greater than or equal to 25% (twenty five percent) increase in HDLc level following a 30

mg/kg dose suggests a compound that can be especially useful for elevating HDLc levels.

It may be particularly desirable to select compounds of this invention that both lower triglyceride levels and increase HDLc levels. However, compounds that either lower triglyceride levels or increase HDLc levels may be desirable as well.

Evaluation of Glucose Levels in db/db Mice

The effects upon plasma glucose associated with administering various dose levels of different compounds of the present invention and the PPAR gamma agonist rosiglitazone (BRL49653) or the PPAR alpha agonist fenofibrate, and the control, to male db/db mice, are studied.

Five week old male diabetic (db/db) mice [for example, C57BlKs/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor, ME] or lean littermates are housed 6 per cage with food and water available at all times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed, and bled via the tail vein for determination of initial glucose levels. Blood is collected (100 µl) from unfasted animals by wrapping each mouse in a towel, cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized capillary tube. Sample is discharged into a heparinized microtainer with gel separator and retained on ice. Plasma is obtained after centrifugation at 4ºC and glucose measured immediately. Remaining plasma is frozen until the completion of the experiment, when glucose and triglycerides are assayed in all samples. Animals are grouped based on initial glucose levels and body weights. Beginning the

following morning, mice are dosed daily by oral gavage for 7 days. Treatments are test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/ 0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice are weighed and bled (tail vein) 3 hours after dosing. Twenty-four hours after the 7th dose (i.e., day 8), animals are bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 are assayed for glucose. After the 24-hour bleed, animals are weighed and dosed for the final time. Three hours after dosing on day 8, animals are anesthetized by inhalation of isoflurane and blood obtained via cardiac puncture (0.5-0.7 ml). Whole blood is transferred to serum separator tubes, chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

Glucose is measured colorimetrically using commercially purchased reagents. According to the manufacturers, the procedures are modified from published work (McGowan, M. W., Artiss, J. D., Strandbergh, D. R. & Zak, B. Clin Chem, 20:470-5 (1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129th Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide for each mole of analyte, coupled with a color reaction first described by Trinder (Trinder, P. Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann Clin Biochem, 6:24 (1969)). The absorbance of the dye produced is linearly related to the analyte in the sample. The assays are further modified in our laboratory for use in

a 96 well format. The commercially available standard for glucose, commercially available quality control plasma, and samples (2 or 5 µl/well) are measured in duplicate using 200 µl of reagent. An additional aliquot of sample, pipetted to a third well and diluted in 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature for 18 minutes for glucose on a plate shaker (DPC Micormix 5) and absorbance read at 500 nm on a plate reader. Sample absorbances are compared to a standard curve (100-800 for glucose). Values for the quality control sample are always within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment are assayed at the same time to minimize inter-assay variability.

Evaluation of the Effects of Compounds of the Present Invention upon A^y Mice Body Weight, Fat Mass, Glucose and Insulin Levels

Female A^y Mice

Female A^y mice are singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the duration of the study. At twenty weeks of age the mice are randomly assigned to vehicle control and treated groups based on body weight and body fat content as assessed by DEXA scanning (N=6). Mice are then dosed via oral gavage with either vehicle or a Compound of this invention (50 mg/kg) one hour after the initiation of the light cycle (for example, about 7 A.M.) for 18 days. Body weights are measured daily throughout the study. On day 14 mice are maintained in individual metabolic chambers for indirect calorimetry assessment of energy expenditure and fuel

utilization. On day 18 mice are again subjected to DEXA scanning for post treatment measurement of body composition.

The results of p.o. dosing of compound for 18 days on body weight, fat mass, and lean mass are evaluated and suggest which compounds of this invention can be especially useful for maintaining desirable weight and/or promoting desired lean to fat mass.

Indirect calorimetry measurements revealing a significant reduction in respiratory quotient (RQ) in treated animals during the dark cycle [0.864 $\pm$ 0.013 (Control) vs. 0.803 $\pm$ 0.007 (Treated); $p < 0.001$] is indicative of an increased utilization of fat during the animals' active (dark) cycle and can be used to selected especially desired compounds of this invention. Additionally, treated animals displaying significantly higher rates of energy expenditure than control animals suggest such compounds of this invention can be especially desired.

Male KK/A^y Mice

Male KK/A^y mice are singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the duration of the study. At twenty-two weeks of age the mice are randomly assigned to vehicle control and treated groups based on plasma glucose levels. Mice are then dosed via oral gavage with either vehicle or a Compound of this invention (30 mg/kg) one hour after the initiation of the light cycle (7 A.M.) for 14 days. Plasma glucose, triglyceride, and insulin levels are assessed on day 14.

The results of p.o. dosing of compound for 14 days on plasma glucose, triglycerides, and insulin are evaluated to

identify compounds of this invention which may be especially desired.

Method to Elucidate the LDL-cholesterol Total-cholesterol and Triglyceride Lowering Effect

Male Syrian hamsters (Harlan Sprague Dawley) weighing 80-120 g are placed on a high-fat cholesterol-rich diet for two to three weeks prior to use. Feed and water are provided ad libitum throughout the course of the experiment. Under these conditions, hamsters become hypercholesterolemic showing plasma cholesterol levels between 180-280 mg/dl. (Hamsters fed with normal chow have a total plasma cholesterol level between 100-150 mg/dl.) Hamsters with high plasma cholesterol (180 mg/dl and above) are randomized into treatment groups based on their total cholesterol level using the GroupOptimizeV211.xls program.

A Compound of this invention is dissolved in an aqueous vehicle (containing CMC with Tween 80) such that each hamster received once a day approx. 1 ml of the solution by garvage at doses 3 and 30 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) is given as a known alpha-agonist control at a dose of 200 mg/kg, and the blank control is vehicle alone. Dosing is performed daily in the early morning for 14 days.

Quantification of Plasma Lipids :

On the last day of the test, hamsters are bled (400 ul) from the suborbital sinus while under isoflurane anesthesia 2 h after dosing. Blood samples are collected into heparinized microfuge tubes chilled in ice bath. Plasma samples are separated from the blood cells by brief centrifugation. Total cholesterol and triglycerides are determined by means of enzymatic assays carried out automatically in the Monarch

equipment (Instrumentation Laboratory) following the manufacturer's precedure. Plasma lipoproteins (VLDL, LDL and HDL) are resolved by injecting 25 ul of the pooled plasma samples into an FPLC system eluted with phosphate buffered saline at 0.5 ml/min through a Superose 6 HR 10/30 column (Pharmacia) maintained room temp. Detection and characterization of the isolated plasma lipids are accomplished by postcolumn incubation of the effluent with a Cholesterol/HP reagent (for example, Roche Lab System; infused at 0.12 ml/min) in a knitted reaction coil maintained at 37°C. The intensity of the color formed is proportional to the cholesterol concentration and is measured photometrically at 505 nm.

The effect of administration of a Compound of this invention for 14 days is studied for the percent reduction in LDL level with reference to the vehicle group. Especially desired compounds are markedly more potent than fenofibrate in LDL-lowering efficacy. Compounds of this invention that decrease LDL greater than or equal to 30% (thirty percent) compared to vehicle can be especially desired.

The total-cholesterol and triglyceride lowering effects of a Compound of this invention is also studied. The data for reduction in total cholesterol and triglyceride levels after treatment with a compound of this invention for 14 days is compared to the vehicle to suggest compounds that can be particularly desired. The known control fenofibrate did not show significant efficacy under the same experimental conditions.

Method to Elucidate the Fibrinogen-Lowering Effect of PPAR Modulators

Zucker Fatty Rat Model:

The life phase of the study on fibrinogen-lowering effect of compounds of this invention is part of the life phase procedures for the antidiabetic studies of the same compounds. On the last (14^{th}) day of the treatment period, with the animals placed under surgical anesthesia, ~ 3ml of blood is collected, by cardiac puncture, into a syringe containing citrate buffer. The blood sample is chilled and centrifuged at 4°C to isolate the plasma that is stored at -70 °C prior to fibrinogen assay.

Quantification of Rat Plasma Fibrinogen:

Rat plasma fibrinogen levels are quantified by using a commercial assay system consists of a coagulation instrument following the manufacturer's protocol. In essence, 100 ul of plasma is sampled from each specimen and a 1/20 dilution is prepared with buffer. The diluted plasma is incubated at 37°C for 240 seconds. Fifty microliters of clotting reagent thrombin solution (provided by the instrument's manufacturer in a standard concentration) is then added. The instrument monitors the clotting time, a function of fibrinogen concentration quantified with reference to standard samples. Compounds that lower fibrinogen level greater than vehicle can be especially desired.

Cholesterol and triglyceride lowering effects of compounds of this invention are also studied in Zucker rats.

Method to Elucidate the Anti-body Weight Gain and Anti-appetite Effects of Compounds of this invention

Fourteen-Day Study in Zucker Fatty Rat[1] or ZDF Rat[2] Models :

Male Zucker Fatty rats, non-diabetic (Charles River Laboratories, Wilmington, MA) or male ZDF rats (Genetic Models, Inc, Indianapolis, IN) of comparable age and weight are acclimated for 1 week prior to treatment. Rats are on normal chow and water is provided ad libitum throughout the course of the experiment.

Compounds of this invention are dissolved in an aqueous vehicle such that each rat received once a day approximately 1 ml of the solution by garvage at doses 0.1, 0.3, 1 and 3 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) a known alpha-agonist given at doses of 300 mg/kg, as well as the vehicle are

controls. Dosing is performed daily in the early morning for 14 days. Over the course of the experiment, body weight and food consumption are monitored.

Using this assay, compounds of this invention are identified to determine which can be associated with a significant weight reduction.

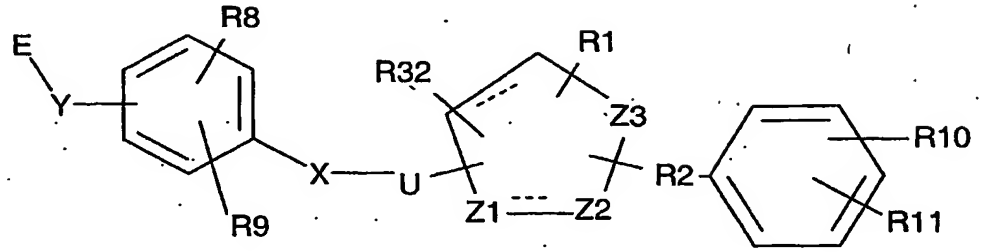
EQUIVALENTS:

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound of the Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl; aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl; heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18,

R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker may be replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with R30;

(f) Y is selected from the group consisting of C, O, S, NH and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, aryloxy,

cycloalkyl and aryl-alkyl are each optionally substituted with from one to three substituents each independently selected from R26;

(h) Z1 and Z2 are each independently selected from the group consisting of N, O, and C with the proviso that at least one of Z1 and Z2 is N;

(i) Z3 is selected from the group consisting of N, O, and C;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are

each optionally substituted with from one to three independently selected from R28;

(m) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo; and

(p) ---- is optionally a bond to form a double bond at the indicated position.

2. A compound as claimed by Claim 1 wherein X is -O-.

3. A compound as claimed by Claims 1 wherein X is -S-.

4. A compound as claimed by any one of Claims 1 through 3 wherein Y is O.

5. A compound as claimed by any one of Claims 1 through 3 wherein Y is C.

6. A compound as claimed by any one of Claims 1 through 3 wherein Y is S.

7. A compound as claimed by any one of Claims 1 through 6 wherein Z3 is N.

8. A compound as claimed by any one of Claims 1 through 7 wherein Z2 is N.

9. A compound as claimed by any one of Claims 1, through 8 wherein Z1 is C.

10. A compound as claimed by any one of Claims 1 through 8 wherein Z1 is N.

11. A compound as claimed by any one of Claims 1 through 8 wherein Z1 is O.

12. A compound as claimed by any one of Claims 1 through 11 wherein ---- is a bond to form a double bond at the designated location on Formula I.

13. A compound as claimed by any one of Claims 1 through 12 wherein E is C(R3)(R4)A.

14. A compound as claimed by any one of Claims 1 through 13 wherein A is COOH.

15. A compound as claimed by any one of Claims 1 through 14 wherein R10 is haloalkyl.

16. A compound as claimed by any one of Claims 1 through 15 wherein R10 is CF_3.

17. A compound as claimed by any one of Claims 1 through 14 wherein R10 is haloalkyloxy.

18. A compound as claimed by any one of Claims 1 through 14 wherein R10 and R11 are each independently selected from the group consisting of hydrogen, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkyloxy.

19. A compound as claimed by any one of Claims 1 through 14 wherein R10 is selected from the group consisting of C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and aryloxy.

20. A compound as claimed by any one of Claims 1 through 19, wherein R8 and R9 are each independently selected from the group consisting of hydrogen and C_1-C_3 alkyl.

21. A compound as claimed by any one of Claims 1 through 20 wherein R1, R2, R3, and R4 are each independently selected from the group consisting of C_1-C_2 alkyl.

22. A compound as claimed by any one of Claims 1 through Claim 20 wherein R1, R3, and R4 are each independently selected from the group consisting of hydrogen and C_1-C_2 alkyl.

23. A compound as claimed by any one of Claims 1 through 20 or Claim 22 wherein R2 is a bond.

24. A compound as claimed by any one of Claims 1 through 23 wherein U is C_1-C_3 alkyl.

25. A compound as claimed by Claim 24 wherein U is saturated.

26. A compound as claimed by any one of Claims 1 through 25 wherein U is substituted with C_1-C_3 alkyl.

27. A compound as claimed by any one of Claims 24, 25 or 26 wherein one carbon is replaced with an -O-.

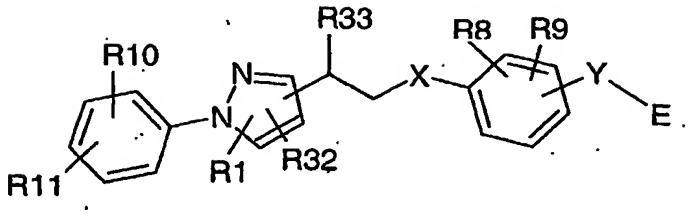
28. A compound as claimed by any one of Claims 1 through 27 wherein "----" each form a double bond in the five membered ring, Z2 and Z3 are each N and Z3 is bonded to R2.

29. A compound as claimed by Claim 28 wherein Y is O and E is $-CH_2COOH$.

30. A compound as claimed by any one of Claims 28 or 29 wherein U is substituted with methyl.

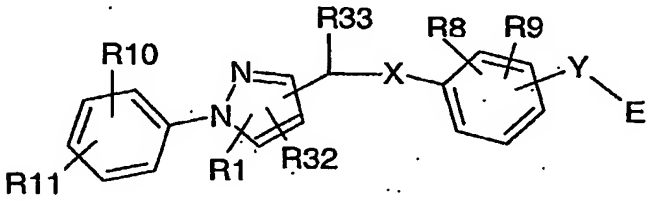
31. A compound as claimed by any one of Claims 28 or 29 wherein U is CH_2.

32. A compound as claimed by any one of Claims 1 through 9, one of Claims 13 through 20, or one of Claims 22,23, 24, 25, 26, 28, 29, or 30 represented by the following Structural Formula II:



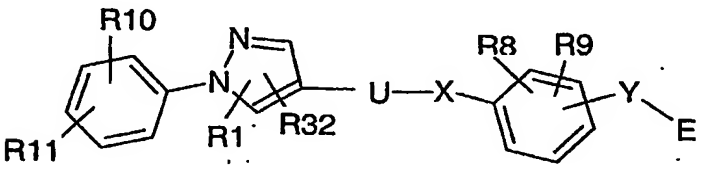
wherein R33 is selected from the group consisting of hydrogen and C_1-C_3 alkyl.

33. A compound as claimed by any one of Claims 1 through 9, or one of Claims 13 through 31 represented by the following Structural Formula III:



wherein R33 is selected from the group consisting of hydrogen and C_1-C_3 alkyl.

34. A compound as claimed by any one of Claims Claims 1 through 9, or one of Claims 13 through 31 represented by the following Structural Formula IV:



35. A compound as claimed by any one of Claims 1 through 34 wherein X and Y are substituted at a 1,4-position, such that X and Y are para substituted to one another.

36. A compound as claimed by any of of Claims 1 through 35 wherein X and Y are substituted at a 1,3-position, such that X and Y are meta substituted to one another.

37. A compound as claimed by Claim 1 wherein the compound is selected from the group consisting of

{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenoxy}-acetic acid;
3-{2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-propionic acid;
(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenoxy)-acetic acid;
(R,S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-propionic acid;
(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;
(R,S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;
(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;
(R,S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;
(R,S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;
(R,S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;
(3-{2-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-acetic acid;
{3-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenyl}-acetic acid;
(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-acetic acid;
2-(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-

pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;
(3-{1-[3-Methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethoxy}-phenyl)-acetic acid;
(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;
(R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;
(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;
(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid;
(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;
(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenyl)-propionic acid;
(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;
(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propoxy}-phenoxy)-acetic acid;
(S)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;
(R)-3-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;
(S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(S)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;

(R)-3-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenyl)-propionic acid;

(S)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

(R)-(2-Methyl-4-{2-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid;

{4-[3,5-Dimethyl-1-(4-trifluoromethyl-phenyl)-2,3-dihydro-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

{4-[1-(3,5-Bis-trifluoromethyl-phenyl)-5-methyl-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenoxy)-acetic acid;

3-(4-{1-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid;

3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid;

{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;

3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-2-methyl-phenyl}-propionic acid;
{3-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid;
3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid;
(S)-3-{4-[5-Chloro-3-isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-2-methoxy-propionic acid;
{3-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-acetic acid;
3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid;
3-{4-[3-Isopropyl-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-ylmethoxy]-phenyl}-2-methoxy-propionic acid;
{2-Methyl-4-[2-(5-methyl-3-phenyl-pyrazol-1-yl)-ethylsulfanyl]-phenoxy}-acetic acid;
[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid;
[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethylsulfanyl)-phenoxy]-acetic acid;
3-[2-Methyl-4-(3-methyl-1-phenyl-1H-pyrazol-4-ylmethoxy)-phenyl]-propionic acid;
{2-Methyl-4-[1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;
{2-Methyl-4-[5-methyl-1-(4-trifluoromethyl-phenyl)-1H-[1,2,3]triazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;
{4-[1-(3,5-Bis-trifluoromethyl-benzyl)-5-phenyl-1H-[1,2,3]triazol-4-ylmethanesulfonyl]-2-methyl-

phenoxy}-acetic acid;
3-(2-Methyl-4-{1-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-yl]-ethoxy}-phenyl)-propionic acid;
3-{2-Methyl-4-[4-methyl-3-(4-trifluoromethyl-phenyl)-isoxazol-5-ylmethoxy]-phenyl}-propionic acid;
{4-[5-Isopropyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid; {4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethylsulfanyl]-2-methyl-phenoxy}-acetic acid;
{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxy]-2-methyl-phenoxy}-acetic acid; and
3-{4-[5-Isopropyl-3-methyl-2-(4-trifluoromethyl-phenyl)-3H-imidazol-4-ylmethoxy]-2-methyl-phenyl}-propionic acid.

38. A compound as claimed by Claim 1 which is a compound of Formula I selected from the group consisting of(R)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid, (S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid, (R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-propylsulfanyl}-phenoxy)-acetic acid, (R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid, and {2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid.

39. A compound as claimed by Claim 1 which is a compound of Formula I selected from the group

consisting of (R,S)-(2-Methyl-4-{1-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid and {2-Methyl-4-[3-methyl-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid.

40. A compound as claimed by any one of Claims 1 through 39 that is the S conformation.

41. A compound as claimed by any one of Claims 1 through 39 that is the R conformation.

42. A pharmaceutical composition, comprising as an active ingredient, at least one compound as claimed by any one of Claims 1 through 41 together with a pharmaceutically acceptable carrier or diluent.

43. A method of modulating a peroxisome proliferator activated receptor, comprising the step of contacting the receptor with at least one compound as claimed by any one of Claims 1 through 41.

44. A method of treating diabetes mellitus in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 41.

45. A method of treating Syndrome X in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 41.

46. A method of selectively modulating a PPAR delta receptor comprising administering a compound as claimed by any one of Claims 1 through 41 to a mammal in need thereof.

47. The manufacture of a medicament for use in the treatment and/or prevention of a condition mediated by nuclear receptors, in particular by a peroxisome

proliferator activated receptor, wherein the compound is a compound as claimed by any one of Claims 1 through 41.

48. A method of treating atherosclerosis in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 41.

49. A compound as Claimed by any one of Claims 1 through 41 for use as a pharmaceutical.

50. A compound as claimed by any one of Claims 1 through 41 wherein the compound is radiolabeled.

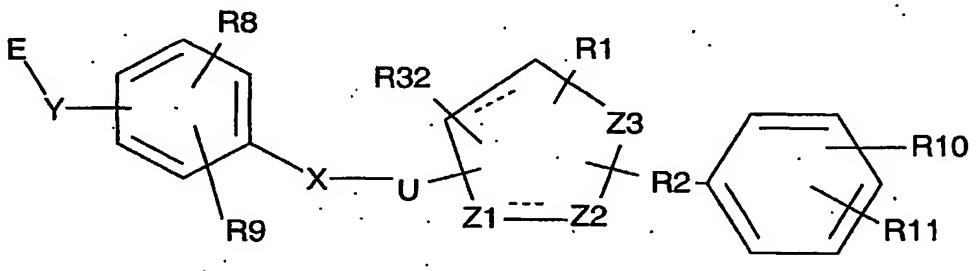
51. A compound as disclosed by any one of the Examples herein.

52. All methods disclosed herein of preparing the compounds represented by Structural Formula I.

PYRAZOLE DERIVATIVE PPAR MODULATORS

ABSTRACT OF THE DISCLOSURE

The present invention is directed to compounds represented by the following structural formula, Formula I:



wherein:

(a) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(b) U is an aliphatic linker;

(c) Y is selected from the group consisting of C, O, S, NH and a single bond;

(d) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide;

(e) Z1 and Z2 are each independently selected from the group consisting of N, O, and C with the proviso that at least one of Z1 and Z2 is N;

(f) Z3 is selected from the group consisting of N, O, and C;

(g) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(h) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29.